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Disorders of CSF Dynamics

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Clinical Features and Diagnosis of Spontaneous Intracranial Hypotension

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ABSTRACT

OBJECTIVE: This article reviews the current understanding of the varied clinical presentations of spontaneous intracranial hypotension and discusses strategies and limitations in diagnosing this complex syndrome, including approaches for medical practitioners outside of specialty centers.

LATEST DEVELOPMENTS: Radiologic algorithms applied to brain MRI (eg, the Bern score) can help assess the probability of an underlying spinal CSF leak, but they do not replace good history-taking and clinical acumen. Brain MRI findings may evolve over time with or without leak-directed treatment. New techniques and improvements in imaging technology have led to better identification and classification of different types of spinal CSF leaks, especially CSF-venous fistulas that were reported for the first time in 2014 and now account for 50% or more of the leaks in patients without spinal extradural fluid collections. Occasionally, spontaneous intracranial hypotension is the result of preexisting intracranial hypertension causing “blowout” leaks.

ESSENTIAL POINTS: Spontaneous intracranial hypotension is caused by leakage of CSF from the spinal dura and most often presents with orthostatic headache, frequently accompanied by neck pain and stiffness, nausea, vestibulo-auditory distortions, visual changes, and other symptoms. Spontaneous intracranial hypotension can be debilitating, and long diagnostic and treatment delays are common. In rare cases, spontaneous intracranial hypotension can have dangerous sequelae, including superficial siderosis, subdural hematoma, bibrachial amyotrophy, brain sagging dementia, and even death. Early recognition of clinical symptoms and radiologic signs is imperative for best patient outcomes.

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INTRODUCTION

Spontaneous intracranial hypotension is an often debilitating and yet treatable condition in which CSF escapes the spinal dura and can cause a wide variety of symptoms, most commonly orthostatic headache but also vestibulo-auditory distortions, dizziness, neck and back pain, and cognitive impairment. Symptoms vary widely among patients and over time. Characteristic radiologic signs are not always present.

Diagnosis requires the recognition of common and uncommon presentations, careful selection and scrutiny of brain and spine imaging, and, frequently, referral to specialist centers.

Spontaneous intracranial hypotension reflects a disruption of the normal continuous production, circulation, and reabsorption of CSF, specifically a loss of CSF from this balanced cycle. Other disorders of CSF dynamics result from disruptions of the cycle at other points (eg, idiopathic intracranial hypertension, normal pressure hydrocephalus, and childhood-onset hydrocephalus, which are discussed in other articles in this issue of *Continuum*). CSF is produced continuously by the choroid plexus in the ventricles of the brain and passes sequentially through the lateral, third, and fourth ventricles before being released into the subarachnoid space that surrounds the entire brain, brainstem, spinal cord, and proximal spinal nerve roots. There is a simultaneous, balanced reabsorption of CSF via arachnoid granulations, primarily into the venous sinuses in the head in adults but, at least in childhood, also through arachnoid granulations on spinal nerve root sleeves that could persist or reopen as collateral routes for CSF escape. More straightforward to conceptualize are the many cases of spontaneous intracranial hypotension that result from simple tearing of the spinal dura that allows the unregulated escape of CSF from the subarachnoid to the extradural space or into the surrounding tissues.

DEFINING SPONTANEOUS INTRACRANIAL HYPOTENSION

Spontaneous intracranial hypotension is currently the most widely used term for the clinical-radiologic syndrome that results when CSF leaks from the thecal sac, but many other names have been used since Schaltenbrand[1] coined the term *aliquorrhea* in 1938 for the clinical syndrome associated with very low lumbar puncture opening pressures (eg, primary intracranial hypotension, intracranial hypovolemia, CSF volume depletion). Despite common use, spontaneous intracranial hypotension is a misnomer because *intracranial hypotension* implies low CSF pressure, and yet more than 50% of patients with this condition have normal and some even high opening CSF pressures.[2] Rather than low pressure, the manifestations of the disorder are better explained based on low CSF volume. Spinal CSF volumes have been estimated radiographically. Patients with spontaneous intracranial hypotension appear to have lower volumes of spinal CSF than healthy controls do, and an increase in the spinal CSF volume after treatment correlates with clinical response.[3-5] Additionally, redistribution of CSF from the spinal to the intracranial compartment after surgical repair of a spinal leak indicates relative intracranial hypovolemia before treatment.[3] Volumetric imaging modalities for diagnosing spontaneous intracranial hypotension are not yet available for clinical use and have not been widely tested in different clinical scenarios.

Spontaneous intracranial hypotension is caused almost exclusively by CSF leakage from the spinal dura, so *spontaneous intracranial hypotension* and *spontaneous spinal CSF leak* are often used interchangeably. Although there may be a history of minor trauma, spontaneous intracranial hypotension specifically excludes lumbar puncture, spine surgery, and other iatrogenic causes of dural breach. Spontaneous intracranial hypotension also does not encompass cranial CSF leaks, which have distinct symptomatology and radiographic presentations[6]; for more information about this entity, refer to the article "Atraumatic Cranial CSF Leaks" by Erin K. O'Brien, MD, and Maria Peris Celda, MD, PhD,[7] in this

KEY POINTS

- **Spontaneous intracranial hypotension results from the escape of CSF from the otherwise balanced cycle of CSF production, circulation, and reabsorption. The underlying cause is CSF leakage at the level of the spine.**

- **The majority of patients with spontaneous intracranial hypotension have normal lumbar puncture opening pressure, and some even have high pressure. The disorder results from reduced CSF volume, not strictly reduced pressure.**

- **Spontaneous intracranial hypotension is caused almost exclusively by CSF leakage from the spinal dura, so *spontaneous intracranial hypotension* and *spontaneous spinal CSF leak* are often used interchangeably.**

- **Head pain in the setting of spinal CSF leak has been attributed to the draining of CSF from the intracranial compartment to the spinal compartment, causing downward traction on pain-sensitive structures such as nerves innervating the dura.**

- **The annual incidence of spontaneous intracranial hypotension is at least 2.9 to 5 per 100,000 and higher in females than males.**

- **The psychological impact of spontaneous intracranial hypotension can be profound, with one survey showing more than 50% of patients with moderate or worse depression, more than 60% expressing a wish to die, and 22% having made a suicide attempt.**

issue of *Continuum*. It has also been suggested that, in some patients with spontaneous intracranial hypotension, CSF does not actually escape the dura but rather pools within a capacious thecal sac because of a very compliant or elastic dura, causing an excessive redistribution of CSF from the cranial to the spinal compartment, resulting in intracranial hypovolemia.[8]

Most spontaneous spinal CSF leakage results from tearing of the dural sac by rubbing against calcified or bony structures, rupture of meningeal diverticula formed around exiting spinal nerves, or development of a fistula from a meningeal diverticulum to the epidural or paraspinal veins. Multiple classification schemes for the subtypes of spinal CSF leaks have been published; these are described in more detail and illustrated in the article “Radiographic Evaluation of Spontaneous Intracranial Hypotension” by Ajay A. Madhavan, MD, and J. Levi Chazen, MD,[9] in this issue of *Continuum*.

MECHANISMS OF SPONTANEOUS INTRACRANIAL HYPOTENSION SYMPTOMATOLOGY

Head pain in the setting of spinal CSF leak has been attributed to the draining of CSF from the intracranial compartment, causing downward traction on pain-sensitive structures such as nerves innervating the dura. Intracranial veins may become engorged to compensate for the lost volume of CSF per the Monro-Kellie doctrine, and this engorgement may also contribute to pain via stretching or compression of small pain-sensitive nerves surrounding the vessels. Diplopia, facial numbness and pain, vestibulo-auditory distortions, and other cranial symptoms have been attributed to the stretching of cranial nerves from downward traction. Vestibulo-auditory symptoms may also be caused by pressure changes in the endolymph and perilymph because they are separated from CSF at some locations only by flexible membranes. Similar mechanisms have been postulated to cause the rarer complications of spontaneous intracranial hypotension and are discussed later in this article.

Although this review focuses on the clinical presentations and diagnosis of spontaneous spinal CSF leaks, when evaluating patients with orthostatic symptoms, persistent and refractory headaches, or other presentations that include spontaneous intracranial hypotension in the differential, it is prudent to ask about any history of potential secondary causes of intracranial hypotension. Examples include trauma causing a tear in the dura (eg, whiplash injuries, rapid chiropractic adjustments) or medical procedures such lumbar punctures, epidurals, and other spinal interventions that could have resulted in chronic iatrogenic spinal CSF leak, especially those that occurred in close temporal proximity to symptom onset. Presentations of these CSF leaks may be similar to chronic spontaneous intracranial hypotension and likely require similar investigative techniques for diagnostic confirmation.

EPIDEMIOLOGY

The annual incidence of spontaneous intracranial hypotension has been reported at 2.9 to 5 per 100,000,[10,11] which is likely an underestimate given the diagnostic challenges and paucity of specialty centers. Females are more likely than males to develop spontaneous intracranial hypotension, at a rate of 1.2:1 to 2:1. The average age of presentation is approximately 45 years, although new diagnoses occur across the entire lifespan. So far, no data on the distribution of cases based on nationality, ethnicity, race, or economic capacity have been published.

TREATMENT DELAYS, DISABILITY, AND IMPACT ON QUALITY OF LIFE

Both diagnosis and treatment of spontaneous intracranial hypotension can be challenging, often requiring expert specialty centers. The lack of awareness of the condition and paucity of providers experienced with the necessary invasive tests and treatments lead to misdiagnoses and delays.[12,13] Symptom severity, including many patients' inability to spend much of the day upright, leads to significant disability and diminished quality of life. In a survey of 64 patients with spontaneous intracranial hypotension in the United Kingdom, more than 25% reported losing their job because of the condition,[14] and more than 66% indicated it affected their financial stability. In another study, 75% of patients with spontaneous intracranial hypotension had severe headache disability scores, and more than 50% had moderate or worse depression. Overall scores of spiritual well-being were similar to patients with acquired immunodeficiency syndrome (AIDS) or cancer, more than 60% had expressed a wish to die, and 22% had made a suicide attempt. In patients who had been treated and were asymptomatic from previous spontaneous intracranial hypotension, scores matched the general population.[15] This condition is largely treatable, and many patients will respond at least temporarily to epidural blood patching, so clinicians can dramatically impact patients' quality of life even before referring patients with more complex or refractory cases to specialty centers.

CLINICAL FEATURES

The most common symptom of spontaneous intracranial hypotension across many reported series over many years is orthostatic headache, which is head pain that is worse when upright and improved when lying flat. There are no specific parameters on the amount of time a patient can spend in a given position before symptoms change and are considered positive. A 2024 study reported that 42% of patients with spontaneous intracranial hypotension had worsening symptoms immediately after becoming upright, 24% after being upright for 1 to 5 minutes, and 19% only after 5 minutes.[16] This same study reported that 44% of patients with spontaneous intracranial hypotension improved within 5 minutes of lying down, 19% in 5 to 15 minutes, and 17% sometime after 15 minutes. Fifteen percent of the patients in the study did not have orthostatic symptoms.[16] Other common patterns of headache in spontaneous intracranial hypotension include triggering or worsening with Valsalva maneuvers and worsening steadily throughout the day. As such, spontaneous intracranial hypotension should be strongly suspected in any patient who describes a new daily persistent headache, especially if there is orthostatic, Valsalva maneuver–related, or second-half-of-the-day worsening (CASE 1-1). Conversely, the orthostatic pattern of headache may be lost over time, and a small percentage of patients with spontaneous intracranial hypotension have no headache at all. A description of a "coat hanger" distribution of pain is not uncommon, with pain at the posterior aspect of the head, radiating into the neck and upper trapezii. A wide range of other symptoms originating from the cranial nerves, vestibular structures, and occasionally the spine are variably seen (TABLE 1-1).

UNCOMMON SYMPTOMS AND SEQUELAE

Spontaneous intracranial hypotension has infrequently been associated with a wide variety of symptoms and sequelae including ataxia,[17,18] bibrachial amyotrophy,[19-21] bulbar palsy,[17,22] cerebral venous sinus thrombosis,[23-25]

KEY POINTS

- **The most common symptom of spontaneous intracranial hypotension is orthostatic headache, which is head pain that is worse when upright and improved when lying flat. Other common patterns include triggering or worsening headache with Valsalva maneuvers or in the second half of the day.**

- **The orthostatic pattern of headache in the setting of spontaneous intracranial hypotension may be lost over time, so patients should be queried about current and past headache patterns. Some patients with spontaneous intracranial hypotension have no headache at all.**

- **Brain sagging dementia resembles behavioral variant frontotemporal dementia, with disinhibition, dysexecutive features, and personality changes more than memory loss. Hypersomnolence is common in these patients. Brain MRI universally shows severe sagging of the hindbrain.**

- **Pachymeningeal enhancement is a helpful diagnostic clue to spontaneous intracranial hypotension but may disappear over time even though symptoms and spinal CSF leakage persist.**

- **A major limitation of the diagnostic criteria for spontaneous intracranial hypotension in the International Classification of Headache Disorders, Third Edition, is the requirement for a headache, which is not present in all patients with spontaneous intracranial hypotension.**

frontotemporal dementia–like syndrome,[26-29] movement disorders,[17,22,30,31] neuroendocrine dysfunction,[32,33] seizures,[34] spinal cord herniation,[35] subarachnoid hemorrhage,[36] superficial siderosis,[21,37] syringomyelia,[38] coma,[39,40] and death[41] (TABLE 1-2). The frequency of these atypical symptoms and sequelae is unknown, but there are more reports of the frontotemporal dementia–like presentation, termed *brain sagging dementia*, than the others mentioned here.

Brain sagging dementia is characterized by behavioral and cognitive changes akin to behavioral variant frontotemporal dementia. Unlike most cases of spontaneous intracranial hypotension in which there is little, if any, correlation between radiographic findings and type or severity of symptoms, in patients with brain sagging dementia there is universal sagging of the hindbrain with swelling of the diencephalon and midbrain (CASE 1-2). Also unlike spontaneous intracranial hypotension in general, brain sagging dementia seems to be male dominant. In a systematic review of patients meeting the proposed criteria for brain sagging dementia, the presenting cognitive and behavioral symptoms included altered speech output, anterograde amnesia, distractibility, impersistence, perseverative and stereotyped behaviors, and a negative alteration in social and interpersonal conduct demonstrating decreased inhibition such as sexual inappropriateness. Unlike behavioral variant frontotemporal dementia, 60% of patients with brain sagging dementia demonstrated cerebellar symptoms such as ataxia, gait disturbance, and dysarthria.[28] Most also have

CASE 1-1

A 30-year-old woman with no significant headache history or general medical history presented to neurology clinic after she lifted her 1-year-old daughter off the floor and felt a pop in her back. She developed a daily holocephalic headache that started in her neck, extended to the occiput, and then spread throughout her entire head. She described it as pressure in her head and tension in her neck and shoulders. The headache was rarely present when she woke in the morning, but it appeared a few minutes after she was out of bed and increased over the day. It was accompanied by nausea, intermittent dizziness, sensitivity to light, and fullness in her ears. Acetaminophen and ibuprofen provided no relief. She was diagnosed with migraine but requested an MRI and referral to a neurologist because the headaches seemed so unusual and severe for her. The finding of smooth, diffuse dural enhancement prompted consideration of spontaneous intracranial hypotension (FIGURE 1-1). A lumbar epidural patch with 25 mL of autologous blood was administered. The patient's headache and other symptoms improved immediately and resolved completely over the next week.

COMMENT

Spontaneous intracranial hypotension should be considered in all patients with new daily persistent headache and sit highest on the differential diagnosis in patients with orthostatic headache. When clinical suspicion is high and supported by brain imaging, nontargeted autologous epidural blood patches can be administered without additional investigation, usually as a single-level lumbar or bilevel low thoracic and lumbar patch.

hypersomnolence, presumably from disruption of the arousal circuits in the thalamus and hypothalamus. Brain sagging dementia can result from any type of spinal CSF leak.

EVOLUTION OVER TIME

Spontaneous intracranial hypotension symptoms and radiologic findings may evolve over time. As previously mentioned, the orthostatic nature of headache diminishes over time for many patients, and thus, it is important to ask about orthostatic worsening both at the time of evaluation and early in the patient's course.[42] The most widely recognized radiologic finding of spontaneous intracranial hypotension, namely diffuse pachymeningeal enhancement, has also been shown to resolve in many patients despite the persistence of a spinal CSF leak.[43] These changes probably reflect physiologic compensatory mechanisms that alter CSF dynamics and have been demonstrated to occur within 3 months of symptom onset.[16] Alternatively, symptoms may worsen, and new symptoms may emerge over time.[16] In a study examining the natural course of spontaneous intracranial hypotension without intervention over at least 6 months, 63% of patients reported stable symptomatology and 65% had stable brain MRI findings.[44] However, 22% of the patients in the study had worsening symptoms whereas 15% reported some improvement; complete resolution was rare. Similarly, the radiographic appearance changed over time with 24% of patients

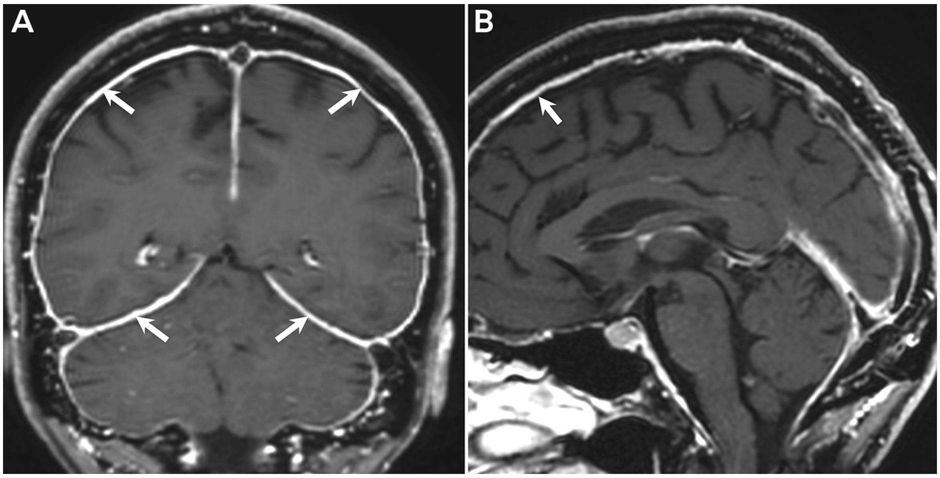

FIGURE 1-1
Imaging findings from the patient in CASE 1-1. Coronal (*A*) and sagittal (*B*) T1-weighted postgadolinium MRI shows diffuse dural enhancement (A, *arrows*; B, *arrow*) that is smooth, nonnodular, and symmetric and involves the supratentorial and infratentorial compartments, consistent with spontaneous intracranial hypotension.

having fewer findings consistent with spontaneous intracranial hypotension on brain imaging over time and 11% having more.[44] It is worth noting that the severity of symptoms and quality of life generally do not correlate with the presence or severity of radiographic findings.

Given lengthy delays in diagnosis and treatment, as well as situations in which patients have clear signs of spontaneous intracranial hypotension but a leak cannot be found, there has been significant interest in whether more severe sequelae are more likely to develop over time in certain patients or if there are predisposing risk factors. Only one published study has explored this question so far.[21] It examined the probability of developing bibrachial amyotrophy, superficial siderosis, or spinal cord herniation over time in 51 patients with spontaneous intracranial hypotension due to ventral dural leaks with associated extradural fluid collections. The authors found a greater than 20% risk of bibrachial amyotrophy (mimicking amyotrophic lateral sclerosis with both upper and lower motor neuron findings on examination) and a 50% risk of superficial siderosis (predominantly infratentorial and presenting with hearing loss or ataxia) at 192 months compared with 0% for either at 48 months, suggesting at least some cases are progressive. No patient in the study developed spinal cord herniation. Because these avoidable complications can cause permanent disability, the authors favor aggressively searching for CSF leaks (including whole-spine MRI and advanced myelography) in cases of unexplained siderosis or amyotrophy, pursuing definitive rather than merely symptomatic treatment and radiographically documenting resolution of spinal extradural fluid collections. Headache may be much less common in these patients, so a high index of suspicion is necessary. No other studies have yet examined the likelihood of developing other severe complications of spontaneous intracranial hypotension over time or in association with particular risk factors.

TABLE 1-1 **Common Symptoms of Spontaneous Intracranial Hypotension**

Symptom	Comment[a]
Headache, head pain or pressure	Most common symptom, not always orthostatic
Vestibulo-auditory changes	Any combination of dizziness, vertigo, phonophobia, aural fullness, tinnitus, hyperacusis, and other hearing disturbance
Cognitive impairment, brain fog	Often persistent or worse later in the day
Visual changes	Photophobia, blurred vision, diplopia, nystagmus, visual loss
Nausea, vomiting	May contribute to misdiagnosis of migraine
Fatigue	Usually multifactorial with contributions from spontaneous intracranial hypotension, chronic pain, reduced daily activity level, and depression or adjustment disorder
Neck or intrascapular discomfort	Often in a "coat-hanger" distribution extending from neck to shoulders
Back pain	Focal or diffuse, may not be representative of CSF leak location

[a] Any symptom may worsen with upright posture, Valsalva maneuvers, or later in the day, and these patterns should prompt increased suspicion for a spinal CSF leak.

DIAGNOSIS OF SPONTANEOUS INTRACRANIAL HYPOTENSION

The most cited diagnostic criteria for spontaneous intracranial hypotension come from the International Classification of Headache Disorders, Third Edition. These criteria are specifically for the headache associated with spontaneous intracranial hypotension, which is a major limitation because, as stated above, not all patients with spontaneous intracranial hypotension have headache.[45] A different set of diagnostic criteria for spontaneous intracranial hypotension proposed by Schievink and colleagues[46] in 2008 is not dependent on headache as a symptom and may be more appropriate. These criteria allow for a diagnosis of spontaneous intracranial hypotension with different levels of confidence based on whether a site of underlying spinal CSF leak has been localized, CSF opening pressure is low, suggestive structural changes of the spinal dura are present, and leak-directed therapies have been helpful. The most definitive radiographic sign of spontaneous intracranial hypotension is extrathecal CSF on spinal imaging. Spontaneous intracranial hypotension and an underlying spinal CSF leak is

Uncommon Symptoms and Sequelae of Spontaneous Intracranial Hypotension

TABLE 1-2

Symptom or sequela	Comment
Cranial nerve palsies	Unilateral or bilateral; manifestations may include dysgeusia, facial numbness and pain, facial spasms and paralysis, dysphagia, and the vestibulo-auditory and visual changes listed in TABLE 1-1
Fever	At onset, spontaneous intracranial hypotension can often mimic aseptic meningitis including mild pleocytosis on CSF analysis
Movement disorders	Tremor, ataxia, tics, parkinsonism, chorea, dystonia
Somnolence and decreased level of consciousness	Ranging from sleepiness and hypersomnolence to rare cases of coma and death
Dementia	Usually frontotemporal dementia–like with obvious midbrain sagging on imaging
Incontinence	Most commonly seen in combination with symptoms of decreased level of consciousness or dementia
Neuroendocrine dysfunction	Including prolactinemia and galactorrhea, central adrenal insufficiency, central hypothyroidism, and central diabetes insipidus
Numbness or paresthesia	Not necessarily in the dermatome corresponding to the spinal level of the leak
Radicular symptoms	Including bibrachial amyotrophy
Syringomyelia	Usually with severe brain sag
Spinal cord herniation	Rare complication of ventral dural tears
Cerebral venous sinus thrombosis	Likely due to slow blood flow through venous sinuses
Subdural hemorrhage	Atraumatic unilateral or bilateral subdural hemorrhage should prompt consideration of spinal CSF leak
Superficial siderosis	Almost exclusively in chronic cases with spinal longitudinal extradural fluid collections

highly likely if cranial imaging shows typical signs and any of the following subcriteria are found: low lumbar puncture opening pressure, spinal meningeal diverticula, or improvement of symptoms after epidural blood patch. Without typical signs on cranial imaging, a patient may still be diagnosed with spontaneous intracranial hypotension if they meet all three subcriteria or have orthostatic headache and two of three subcriteria (TABLE 1-3).

Lumbar Puncture Opening Pressure

Opening pressure measured by lumbar puncture in lateral decubitus position is considered low if less than 6 cm H_2O and can help confirm a diagnosis of spontaneous intracranial hypotension, but the majority of patients with active spinal CSF leaks have normal opening pressure.[2] As such, normal or even high opening pressure does not rule out spontaneous intracranial hypotension. Intracranial pressure monitoring might be more consistent and less prone to inaccurate single-point-in-time measures of CSF pressure, but intracranial

CASE 1-2

A 63-year-old man with controlled hypertension and hyperlipidemia presented to neurology clinic with cognitive decline and personality changes over 6 months. His wife reported numerous inappropriate comments to her and in public. He had become less caring and increasingly unmotivated. He was sleeping 16 to 18 hours per day, and he lost his job as a computer engineer after missing several deadlines. His primary physician diagnosed him with dementia and referred him to a neurologist. On direct questioning, he reported neck pain and daily mild headaches without clear postural worsening, but he was unable to recall a precise onset of symptoms.

Brain MRI (FIGURE 1-2) showed severe brain sagging with slumping of the pons against the clivus, a severely reduced mamillopontine distance, downward drooping of the splenium of the corpus callosum, and cerebellar tonsillar ectopia but no significant atrophy of the frontal or temporal lobes. He was diagnosed with brain sagging dementia and referred to a specialist center. Myelography revealed a CSF-venous fistula at T2, which was treated by transvenous embolization. The patient's cognitive and behavioral changes resolved within 1 month of treatment.

COMMENT

All patients with symptoms of dementia should undergo brain imaging, preferably MRI. Symptoms and radiographic signs of brain sagging dementia are usually reversible with treatment of the underlying spinal CSF leak. Brain MRI should be repeated 1 to 3 months after leak treatment to establish a new radiographic baseline at a time when the patient feels well. Patients with brain sagging dementia should be referred to a specialty clinic for advanced myelography and targeted leak treatment. Nontargeted epidural blood patching can be attempted but should not replace expedited referral for more definitive management of the spinal CSF leak underlying the dementing syndrome.

pressure monitoring is invasive, normal intracranial pressures may still be found in patients with active CSF leaks, and, ultimately, this is a disorder of low CSF volume, not low pressure. We do not yet have widely available tools to measure total CSF volume. Neither lumbar puncture nor intracranial pressure monitoring alone is recommended as part of the routine evaluation of patients with spontaneous intracranial hypotension.

Radiographic Findings

The diagnosis of spontaneous intracranial hypotension relies heavily on radiographic imaging; refer to the article "Radiographic Evaluation of Spontaneous Intracranial Hypotension" by Ajay A. Madhavan, MD, and J. Levi Chazen, MD,[9] in this issue of *Continuum*. Only a brief review of key imaging findings is provided here, focusing on the most helpful signs for the clinician investigating the primary diagnosis of spontaneous intracranial hypotension (as opposed to the precise localization of the underlying spinal CSF leak, which often

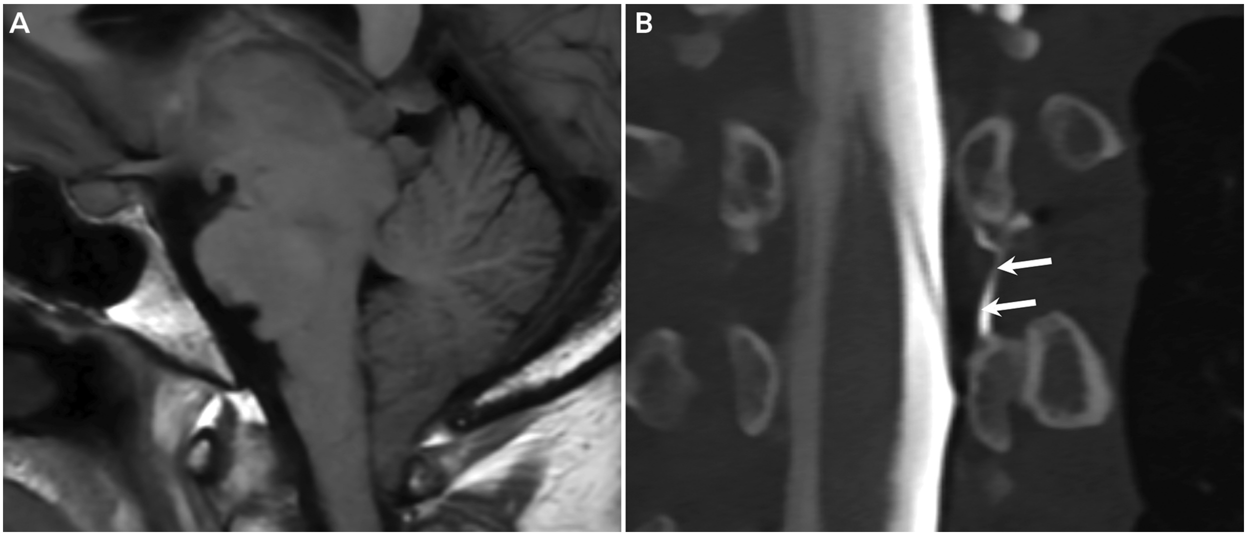

FIGURE 1-2
Imaging findings from the patient in CASE 1-2. *A*, Sagittal T1-weighted MRI shows severe brain sagging with distortion and swelling of the upper brainstem. *B*, Coronal reconstruction from a photon-counting CT myelogram shows a left T2 CSF-venous fistula (*arrows*) as the cause of spontaneous intracranial hypotension.

requires referral to a specialty center). It cannot be repeated too often that brain MRI changes in the setting of spontaneous intracranial hypotension can be subtle, even when symptoms are severe, and that MRI may be completely normal in up to 20% of these cases.

Brain MRI for suspected spontaneous intracranial hypotension should include precontrast and postcontrast images in axial, sagittal, and coronal planes. The intracranial imaging findings typical for spontaneous intracranial hypotension are recalled by the mnemonic SEEPS: **s**ubdural fluid collections, **e**nhancement of meninges, **e**ngorgement of venous structures, **p**ituitary hyperemia, and **s**agging of the brain (**FIGURE 1-3**). Smooth, non-nodular, diffuse pachymeningeal enhancement is essentially pathognomonic for spontaneous intracranial hypotension, but all of the other findings can be present in other conditions or sometimes in healthy patients. Pachymeningeal enhancement, involving only the outer layer of dura mater, must be distinguished from leptomeningeal enhancement, which involves the arachnoid and pia layers and, thus, tracks along the surfaces of gyri and sulci. Most infectious, inflammatory, and neoplastic causes of meningeal enhancement manifest as leptomeningeal enhancement alone or as combined pachymeningeal and leptomeningeal enhancement that is lumpy and focal or multifocal, whereas spontaneous intracranial hypotension causes pure pachymeningeal enhancement that is smooth and symmetric throughout the supratentorial and infratentorial compartments. Although dural enhancement is the most frequently reported intracranial radiographic finding in spontaneous intracranial hypotension, it is not always present and may resolve over time.[47] Postcontrast three-dimensional and brain volume MRI sequences often generate a false appearance of smooth diffuse dural enhancement.

TABLE 1-3

Schievink Diagnostic Criteria for Spontaneous Spinal CSF Leak and Intracranial Hypotension[a]

Criterion A

Demonstration of a spinal CSF leak (ie, presence of extradural CSF)

Or, if criterion A is not met, then

Criterion B

Cranial MRI changes of intracranial hypotension (ie, presence of subdural fluid collections, enhancement of the pachymeninges, or sagging of the brain) and at least one of the following

1. Low opening pressure (≤6 cm H_2O)
2. Spinal meningeal diverticulum
3. Improvement of symptoms after epidural blood patching

Or, if criteria A and B are not met, then

Criterion C

All three B criteria, or orthostatic headache plus any two B criteria

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[a] Reprinted with permission from Schievink WI, et al, AJNR Am J Neuroradiol.[46] © 2008 American Society of Neuroradiology.

The Monro-Kellie doctrine dictates that loss of CSF from the cranium must be compensated by an increase in the volume of brain tissue or intracranial blood, and this explains the components of SEEPS as well as many lesser-known (and variably reliable) radiographic signs in spontaneous intracranial hypotension. Subdural fluid collections can be hematomas or hygromas, unilateral or bilateral, and symptomatic or asymptomatic. They occur between cellular layers of the dura (though traditionally referred to as subdural), so contrast enhancement may be seen on both the skull and brain surfaces of the fluid collections. The discovery of a subdural fluid collection in a patient with headache or other symptoms of spontaneous intracranial hypotension and without a history of head trauma should be investigated for possible spontaneous spinal CSF leak (CASE 1-3). Venous engorgement is best appreciated as a convex and downward bowing of the inferior margin of the transverse sinuses and outward bowing of the lateral margins of the superior sagittal sinus. Pituitary hyperemia results in pituitary enlargement, upward bowing of the superior margin of the gland, and reduced height of the suprasellar cistern. Brain sagging may involve the floor of the third ventricle (further reducing the height of the suprasellar cistern), brainstem (obliterating the prepontine cistern), and cerebellar tonsils (a nonspecific finding that should not be confused with Chiari malformation).

Of many studies that have evaluated qualitative and quantitative markers of spontaneous intracranial hypotension on cranial imaging, the brain spontaneous intracranial hypotension score, or the Bern score, reported by Dobrocky and colleagues[48] in 2019, has become the most widely used. The Bern score comprises six variables to generate a score from 0 to 9, with higher scores indicating a higher likelihood of finding a spinal CSF leak on myelography. Although a high Bern score strongly predicts the presence of a spinal CSF leak, it does not correlate with clinical severity and should not be used as a marker of clinical wellness or malady.[49] Another marker of spontaneous intracranial hypotension, layered calvarial hyperostosis, is seen in approximately 32% of patients who have spontaneous intracranial hypotension.[50] Although it is not as prevalent as many

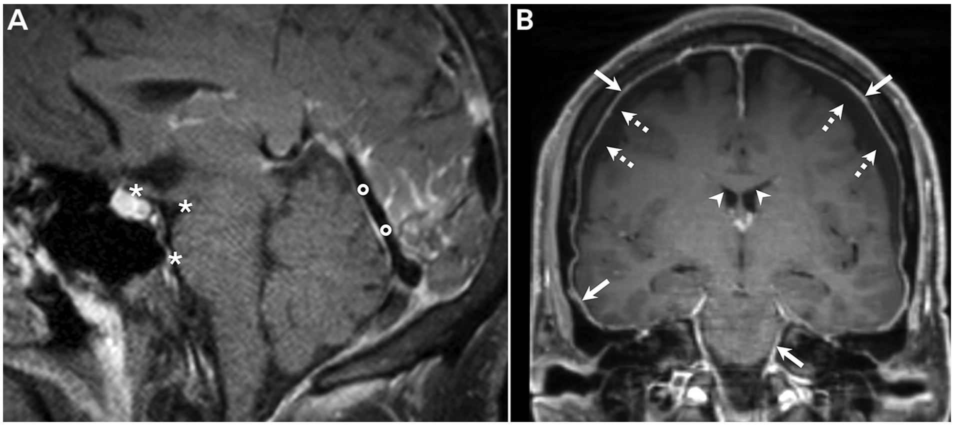

FIGURE 1-3
Brain MRI showing most of the signs of spontaneous intracranial hypotension. *A*, Sagittal T1-weighted image shows brain sag (*asterisks*) with reduced suprasellar cistern, prepontine cistern, and mamillopontine distance, as well as venous engorgement (*circles*). *B*, Coronal postgadolinium T1-weighted image shows diffuse dural enhancement (*solid arrows*), bilateral subdural fluid collections (*dashed arrows*), and small ventricular caliber (*arrowheads*). The total Bern score for this patient is 9/9.

KEY POINTS

- **Because CSF pressure is normal in most patients with spontaneous intracranial hypotension, standalone lumbar puncture or intracranial pressure monitoring is not recommended as part of the routine evaluation of spontaneous intracranial hypotension.**

- **The severity of brain MRI changes does not correlate with the severity of patients' symptoms in spontaneous intracranial hypotension, and brain MRI may be completely normal in up to 20% of cases.**

- **Brain MRI with more signs of spontaneous intracranial hypotension (ie, a higher Bern score) strongly predicts the presence of a spinal CSF leak, but it does not correlate with clinical severity.**

- **Radioisotope cisternography has excellent sensitivity for the presence of an underlying spinal CSF leak of any type, which can be helpful when the clinical history is suggestive but brain MRI is normal, but it has poor spatial resolution and, thus, poor localizing value for the underlying leak.**

of the MRI findings, hyperostosis is also visible on CT and, thus, may be useful in settings with limited access to MRI.

When spine MRI demonstrates extradural CSF, not only is the diagnosis of spontaneous intracranial hypotension established, but the type of underlying leak (dural tear) has been determined. Caution must be taken not to confuse T2-hyperintense epidural fat for fluid. Meningeal diverticula are dilations of the dural sleeves that surround spinal nerve roots. Sometimes they are called perineural cysts, but they are not proper cysts in that they are not completely walled-off fluid collections. They are potentially weak or thin regions of dura prone to leaking or fusing with epidural veins to create CSF-venous fistulas. Such diverticula are common in patients with spontaneous intracranial hypotension but also in the general population.[51] Larger and more complex diverticula are

CASE 1-3

A 70-year-old man with no history of headache presented to neurology clinic with severe head pain each time he coughed. He had no history of trauma or whiplash injury. He had hyperlipidemia and mild gastroesophageal reflux disease but no other medical history. He took atorvastatin daily, used omeprazole infrequently, and avoided nonsteroidal anti-inflammatory drugs because of his gastroesophageal reflux disease. His headaches were bifrontal and could last up to 2 hours depending on how much he coughed. Other Valsalva maneuvers such as sneezing or bending forward triggered similar headaches. The headaches were not associated with nausea, vomiting, photophobia, or phonophobia. His neurologic examination was normal.

Brain MRI without contrast showed bilateral subdural hematomas without compression of the underlying brain (FIGURE 1-4). MR angiography and MR venography showed normal intracranial vasculature. Serum markers for clotting and bleeding diathesis were normal. The hematomas were drained via burr holes, but the headaches persisted. After 3 months, he was still having cough-related headaches and was referred to a neurologist. Repeat MRI revealed recurrent subdural hematomas bilaterally. Careful comparison with his MRIs at presentation revealed dural thickening, venous engorgement, and the aforementioned subdural fluid collections (Bern score, 5/9), raising suspicion for spontaneous intracranial hypotension. Spine MRI showed ventral extradural fluid with MRI characteristics of CSF. A prone dynamic CT myelogram showed a ventral CSF leak due to a disk osteophyte protruding through the dura at T1-T2. The cough-related headache resolved with surgical repair of the CSF leak and resection of the osteophyte to reduce the risk of leak recurrence.

COMMENT

An underlying spinal CSF leak should be considered in any case of atraumatic subdural hematoma or hygroma. Subdural fluid collections often recur if the underlying leak is not treated. Surgical evacuation of hematomas or hygromas due to spontaneous intracranial hypotension is generally not necessary if the spinal CSF leak can be found and sealed.

more likely to leak, but patients frequently have multiple diverticula, and it is not always the largest one that harbors the leak or fistula. The presence of spinal diverticula in a patient with orthostatic headache or other symptoms suggestive of spontaneous intracranial hypotension should prompt the clinician to investigate further or refer on, even if brain MRI is normal or only minimally abnormal.

Radioisotope cisternography, wherein a radioactive tracer is injected by standard lumbar puncture and then observed with a nuclear medicine detector to migrate up the spinal column and over the cerebral convexities over the course of 24 hours, can be helpful in cases in which there is clinical suspicion for spontaneous intracranial hypotension but no supportive findings on brain or spine MRI. Although nuclear cisternography has poor localizing value for spinal

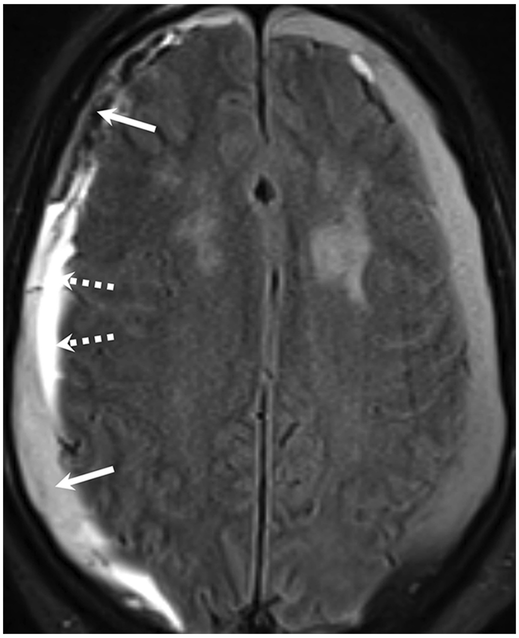

FIGURE 1-4

MRI findings from the patient in CASE 1-3. Axial fluid-attenuated inversion recovery (FLAIR) image shows bilateral subdural fluid collections. On the left side of the image, the mixed signal intensities reflect the mixed composition of the collection with regions of blood (*solid arrows*) and CSF (*dashed arrows*).

CSF leaks, reduced or absent tracer activity over the cerebral convexities 24 hours after injection is a very sensitive sign for the presence of a spinal leak of any type. Other indirect evidence of a spinal CSF leak is the early appearance of tracer in the urinary bladder (4 hours or less after injection) or diffuse systemic tracer activity (silhouette sign), indicating vascular uptake and circulation.[52] Clear communication between the clinician evaluating possible spontaneous intracranial hypotension and the radiologist performing the cisternogram is important so that images are acquired at proper intervals to yield meaningful interpretations of CSF dynamics.

Other biomarkers or tests for spontaneous intracranial hypotension that have been reported or are under active investigation include CSF total transferrin,[53] otoacoustic measurements,[54] optic nerve sheath diameter by ultrasonography,[55] spinal dural compliance testing,[56] lamina cribrosa thickening in the absence of glaucoma,[57] and MR elastography.[58] Routine CSF constituents are usually normal, but pleocytosis up to 222 cells/mm^3 and elevated protein as high as 1000 mg/dL have been reported.[59,60] There is no blood test for spinal CSF leak. β-2 transferrin, which can be used to test some body fluids for the presence of CSF, cannot be reliably assayed in blood. A pragmatic approach to suspected spontaneous intracranial hypotension is shown in **TABLE 1-4**.

RISK FACTORS

Connective tissue disorders such as Marfan syndrome and disorders of joint hypermobility are often purported to be associated with spontaneous intracranial

TABLE 1-4

Guiding Principles of Spontaneous Intracranial Hypotension Diagnosis and Management

Is this patient's clinical story suggestive of spontaneous intracranial hypotension?

- Depends on recognizing common and uncommon symptoms of spontaneous intracranial hypotension and risk factors

Are there cranial imaging findings of spontaneous intracranial hypotension?

- Requires careful assessment of brain MRI without and with gadolinium contrast for stigmata of intracranial CSF volume depletion; if MRI is normal, radioisotope cisternography should be considered

Are there spine MRI findings to suggest a specific type of underlying CSF leak?

- Search for a spinal longitudinal extradural fluid collection (SLEC) on MRI of the entire spine without contrast, best seen with heavily T2-weighted fat-saturated sequences; these are most often ventral but occasionally are lateral, dorsal, or circumferential; the presence of an SLEC indicates a type 1 (dural tear) leak; the absence of an SLEC implies a leaking meningeal nerve root sleeve diverticulum or, more often, CSF-venous fistula

Where is the CSF leak?

- Requires an appropriately chosen and well-performed myelogram; SLEC-positive leaks require myelography with excellent spatial and temporal resolution for localization; SLEC-negative leaks and fistulas are best seen on digital subtraction myelography or dynamic CT myelography in the lateral decubitus position

What treatment should be offered?

- Answers vary depending on leak type, leak location, patient preference, and resources available in the given clinical context (eg, clinician experience and available resources; provider preference toward surgery versus interventional radiology techniques) hypotension, and several prospective studies have reported high frequencies of patients with features of connective tissue disorders ranging from 18% to 38%.[61-64] In the only study exploring the relationship between spontaneous intracranial hypotension and connective tissue disorders that used a control group, however, there was very little difference in connective tissue abnormalities between the groups.[64] The one exception was dolichostenomelia (ie, disproportionately long arms), which was seen significantly more frequently in the spontaneous intracranial hypotension group.[64] Thus, it is unclear if connective tissue disorders and joint hypermobility disorders are truly risk factors for spontaneous intracranial hypotension. Notably, connective tissue disorders and joint hypermobility are reported risk factors for both migraine and postural orthostatic tachycardia syndrome, which are common mimics of spontaneous intracranial hypotension.[65] Other risk factors include disk osteophytes in the spine[66] (the usual cause of ventral dural tears, but these are exceedingly common also in patients without CSF leak), bariatric surgery[63] (extreme central weight loss probably augments the pressure differential between spinal CSF and paraspinal veins, thus promoting CSF-venous fistula formation), and intracranial hypertension (whether primary or secondary intracranial hypertension, high CSF pressure may "self-treat" through the opening of a spontaneous CSF leak at the level of the skull base or the spine; refer to the article "Atraumatic Cranial CSF Leaks" by Erin K. O'Brien, MD, and Maria Peris Celda, MD, PhD,[7] in this issue of *Continuum*).

SPECIAL POPULATIONS

Little has been published regarding spontaneous intracranial hypotension in specific patient populations such as pregnant or pediatric patients. Several reports of spontaneous intracranial hypotension in pregnancy (not iatrogenic leaks caused by epidural anesthesia) have documented safe labor and delivery of healthy infants with a variety of treatment modalities including conservative measures and autologous epidural blood patching. The relatively high radiation doses associated with digital subtraction and CT myelography generally mean the search for the site of spinal CSF leakage cannot occur during pregnancy, and treatment options are only those that can be performed with minimal imaging guidance such as nontargeted lumbar epidural blood patch. In one reported case in which spontaneous intracranial hypotension preceded pregnancy, symptoms improved during pregnancy until 2 months postpartum, and the improvement was postulated to be from increased abdominal pressures causing tamponade and thereby increasing CSF pressures.[67] A 2024 multi-institution series of 12 pediatric patients (age range 9 to 17 years at symptom onset) highlights that advanced myelography was successfully performed in each case, precisely localized a CSF leak in all cases (including lateral dural tears, CSF-venous fistulas, and one ventral dural tear), and facilitated targeted treatment with dramatic symptomatic improvement in at least 11 of 12 children.[68] Spontaneous spinal CSF leaks are most common in midadulthood but can occur at any age, and the clinician faced with a patient with symptoms suggestive of spontaneous intracranial hypotension should pursue the diagnosis regardless of age.

MIMICS, COMORBIDITIES, AND MISDIAGNOSES

Because patients with spontaneous intracranial hypotension most often present with headache, the most common misdiagnoses are other headache disorders,

CASE 1-4

A 24-year-old woman, a ballet dancer, presented to neurology clinic for worsening headache in the setting of new lightheadedness and exercise intolerance and had a history of chronic migraine without aura responsive to calcitonin gene-related peptide monoclonal antibody therapy and anxiety controlled with a low-dose selective serotonin reuptake inhibitor (SSRI). She reported getting a low-grade headache shortly after getting out of bed in the morning that increased throughout the afternoon and was consistently worse in the evening. It was similar to her typical migraine except that triptans no longer helped. She rarely woke with a headache but could develop a severe migraine about 2 days per week, more likely if she tried to be more physically active. Her headache intensity was reduced by about half with recumbency. She developed new tinnitus, palpitations, upper-extremity paresthesia, and depression.

Neurologic examination was normal, and her Beighton Hypermobility Score was 7/9. She had mild tachycardia in the office and reported that her resting heart rate was always 55 to 60 beats/min before the worsening of her headaches. Referral to a cardiologist resulted in tilt-table testing consistent with postural orthostatic tachycardia syndrome (POTS) without other cardiac concerns. Management of POTS did not help her second-half-of-the-day headaches. Brain MRI with and without contrast revealed mild effacement of the suprasellar and prepontine cisterns with normal mamillopontine distance and no venous engorgement. Her Bern score was 3/9. Full-spine MRI showed spinal diverticula at multiple levels (FIGURE 1-5). She was referred to a specialist center where a CSF-venous fistula was found and embolized. Her second-half-of-the-day headaches improved but were not entirely eliminated, and her migraine frequency was reduced but not to the previous best management until she reincorporated the POTS treatment strategies that had not been effective when she was also leaking CSF.

COMMENT

Consider spontaneous intracranial hypotension in patients without an alternative explanation for worsening of previously stable headache or migraine, especially if there is new orthostatic, Valsalva maneuver–related, or second-half-of-the-day exacerbation of symptoms. Patients can have comorbid migraine and spontaneous intracranial hypotension. POTS may precede spontaneous intracranial hypotension or develop with it, and these diagnoses are not mutually exclusive. Subtle findings on MRI such as brain sagging measurements used to calculate the Bern score may be overlooked by some radiologists at nonspecialty centers. Effective treatment of spinal CSF leak does not always return patients fully to their preleak baseline for several reasons. Symptomatic treatment of headache should be continued, and a reevaluation for a spinal CSF leak may be necessary.

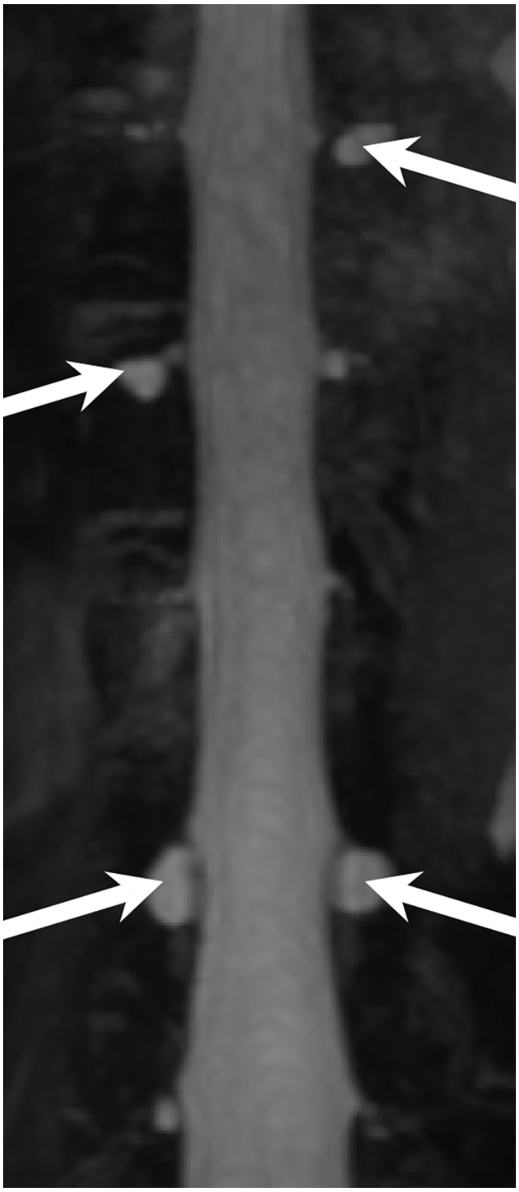

FIGURE 1-5

MRI findings from the patient in CASE 1-4. Coronal maximal intensity projection T2-weighted fast spin echo image shows multiple meningeal nerve root sleeve diverticula (*arrows*) in the thoracic spine with no associated extradural fluid collection.

such as chronic migraine, vestibular migraine, posttraumatic headache, cervicogenic headache, and new daily persistent headache. New daily persistent headache is a recognized diagnosis in the International Classification of Headache Disorders, Third Edition, but it amounts to a syndromic diagnosis and should prompt further testing (at least brain MRI without and with gadolinium contrast) to look for signs of spontaneous intracranial hypotension. Migraine may be comorbid with spontaneous intracranial hypotension and exacerbated by pain activation of trigeminal or cervical sensory afferent nerves, becoming refractory to migraine-directed therapies at least as long as there is active CSF leakage.

Chiari malformation is a common misdiagnosis in patients with spontaneous intracranial hypotension because Valsalva maneuver–induced headache and tonsillar ectopia can be seen in both disorders, but the pathophysiologies are different and the implications of misdiagnosis and mistreatment can be extreme. Although Chiari malformation is a congenital structural defect whereby a too-small posterior fossa becomes overcrowded and the cerebellar tonsils are forced down through the foramen magnum, spontaneous intracranial hypotension is an acquired disorder in which loss of CSF means the brainstem and cerebellum sink from their usual position and settle down through the foramen magnum. The appearance of the floor of the third ventricle and the upper brainstem may assist in distinguishing Chiari malformation from spontaneous intracranial hypotension.[69] A cervical syrinx can be present in both disorders. If a patient with spontaneous intracranial hypotension and cerebellar tonsillar ectopia undergoes posterior fossa decompression, the result is an even larger cranial vault, an even greater relative deficit of CSF, and worsening of brain sagging and spontaneous intracranial hypotension symptoms.

Certain autonomic disorders, namely neurogenic orthostatic hypotension and postural orthostatic tachycardia syndrome, because of their patterns of upright posture triggering symptoms, may be confused for or coexist with spontaneous

TABLE 1-5 **Clinical Mimics and Confounders of Spontaneous Intracranial Hypotension**

Clinical mimic	Distinguishing features	Spinal CSF leak
Orthostatic hypotension	Autonomic failure, medication effect, hypovolemia	Stable blood pressure with postural changes
Postural orthostatic tachycardia syndrome	Excessive increase in heart rate despite stable blood pressure on standing	Stable heart rate with postural changes
Chiari malformation	Headache triggered by cough and other Valsalva maneuvers but not upright posture, lasting seconds to minutes	MRI shows cerebellar tonsillar ectopia and sagging of other brainstem structures, with or without cervical syrinx
Cervicogenic headache	Headache with neck pain that worsens with cervical motion regardless of upright or recumbent posture, relieved with medication	Head more than neck pain worsened more by upright posture than cervical motion, not relieved with medication
Vestibular migraine	Vertigo, unilateral headache, nystagmus, presence of aura, history of migraine	Hearing changes and tinnitus more than vertigo or nystagmus
Persistent postural perceptual dizziness	Waxing and waning dizziness, exacerbated by upright posture, motion, and visual stimuli	Headache more than dizziness, triggered by upright posture and Valsalva maneuvers

intracranial hypotension (**CASE 1-4**). Because vestibulo-auditory symptoms are so often part of spontaneous intracranial hypotension, other vestibular disorders may be suspected instead of spontaneous intracranial hypotension. **TABLE 1-5** lists common clinical mimics of spontaneous intracranial hypotension and key features that distinguish them.

DIAGNOSITIC CAVEATS

There has been a significant increase in spontaneous intracranial hypotension research in the past 10 years, which has increased awareness of this disabling disorder and our skills in localizing and treating the causative spinal CSF leaks, but this work has also revealed some of the flaws on which our diagnoses and research have been based. Of particular importance are the realizations that CSF opening pressure is low in only a minority of patients and that CSF-venous fistulas, which generally cannot be detected on conventional spine MRI or traditional CT myelography, are present in a large portion (perhaps the majority) of patients with spontaneous intracranial hypotension who do not have extradural CSF on spine MRI. Thus, many publications before 2014 were based on the evaluation of a subset of patients with spontaneous intracranial hypotension with large, easily detectable extradural fluid collections and low opening CSF pressures. Additionally, we have learned that compensatory alterations of CSF dynamics may diminish or augment orthostatic features and some MRI features over time, suggesting that perhaps we should be analyzing signs and symptoms of spontaneous intracranial hypotension according to “time-since-symptom onset” in each study. For example, clinical experience tells us that cognitive symptoms are commonly reported by patients with spontaneous intracranial hypotension. In a 2021 large meta-analysis with an average symptom duration of 32 days, however, cognitive impairment was an infrequent symptom (2.6%).[70] In a 2023 study in which 73% of patients had symptoms for more than 3 months, in contrast, cognitive and memory symptoms were reported by more than one-half of the patients.[71] Selection bias has probably influenced our understanding of spontaneous intracranial hypotension and may persist as long as large meta-analyses (often the highest level of evidence available for relatively rare diseases such as spontaneous intracranial hypotension) continue to include older studies in which practitioners relied more on low opening pressures and obvious imaging findings and before the recognition of CSF-venous fistulas. With recent advances in diagnostic imaging,[72] more interest and research into spontaneous intracranial hypotension, increased health care provider exposure to the condition, and a new international patient registry for spinal CSF leak that is being created, we are likely to gain a much greater understanding of spontaneous intracranial hypotension.

KEY POINTS

- **Spontaneous spinal CSF leaks are most common in midadulthood but can occur at any age.**
- **Spontaneous intracranial hypotension is often misdiagnosed as another headache disorder. New daily persistent headache, in particular, should raise suspicion for an underlying spinal CSF leak.**

CONCLUSION

Spontaneous intracranial hypotension and spinal CSF leak can present with a wide array of symptoms that may evolve over time, improving in some and worsening in others. Orthostatic headache is the hallmark of spontaneous intracranial hypotension, but cases without this feature should not be overlooked. Patients with untreated spontaneous intracranial hypotension have significant disability, and diagnostic and treatment delays can result in significant harm to patients' physical, mental, and financial well-being. Diagnosis of spontaneous intracranial hypotension should be clinically driven and radiologically confirmed. In cases with high clinical suspicion and minimal radiologic signs on brain and spine MRI with a protocol for spinal CSF leak, empiric blood patching and referral to a specialist center for further evaluation are warranted. Diagnosis and treatment of spontaneous intracranial hypotension requires a team effort among neurologists, radiologists, surgeons, anesthesiologists, and specialist CSF centers. Although spontaneous intracranial hypotension can often be cured with blood patches, embolization, or surgery alone or in combination, recurrence is possible (refer to the article "Treatment of Persistent Headache After Normalization of CSF Pressure" by Olga Fermo, MD,[73] in this issue of *Continuum*), as is development of symptoms representative of a high-pressure state (rebound intracranial hypertension) after treatment. Follow-up after treatment is imperative, and repeat evaluation and treatment may be necessary. Spontaneous intracranial hypotension has myriad presentations, and attentive care by neurologists can alleviate considerable effects caused by this disorder.

USEFUL WEBSITES

Three international foundations provide accurate and up-to-date patient education materials and support. They host medical provider and patient conferences most years and support research related to spontaneous intracranial hypotension.

Spinal CSF Leak Foundation (United States)
spinalcsfleak.org

Spinal CSF Leak Foundation Canada
www.spinalcsfleakcanada.ca

CSF Leak Association (United Kingdom)
csfleak.uk

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Radiographic Evaluation of Spontaneous Intracranial Hypotension

By Ajay A. Madhavan, MD; J. Levi Chazen, MD

ABSTRACT

OBJECTIVE: Diagnostic imaging evaluation for patients with suspected spontaneous intracranial hypotension has evolved substantially in recent years. This article describes a practical algorithm for radiographic diagnosis of spontaneous intracranial hypotension and localization of spinal CSF leaks.

LATEST DEVELOPMENTS: Brain and spine MRI is the mainstay of the initial diagnostic workup of patients with spontaneous intracranial hypotension. Recently, sophisticated myelographic techniques to precisely subtype and localize CSF leaks have been developed and refined. These include fluoroscopic techniques, such as digital subtraction myelography, and CT-based techniques, such as hyperdynamic CT myelography. These techniques improve the detection of various types of CSF leaks, thereby enabling targeted therapies.

ESSENTIAL POINTS: Neurologists should familiarize themselves with the variety of imaging necessary to initially support a diagnosis of spontaneous intracranial hypotension and the myelographic techniques needed to precisely localize spinal CSF leaks.

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Drs Madhavan and Chazen discuss the unlabeled use of intrathecal administration of gadolinium for myelography.

INTRODUCTION

Multiple classification schemes have been developed to subtype spinal CSF leaks, which are the cause of spontaneous intracranial hypotension. In 2016, Schievink and colleagues[1] proposed one such classification scheme that includes ventral dural tears (type 1a), posterolateral dural tears (type 1b), leaking meningeal diverticula (type 2), and CSF-venous fistulas (type 3). Another classification scheme suggested by Farb and colleagues[2] encompasses the same pathology with slightly different numbering.[2] Although spontaneous intracranial hypotension is typically caused by a single spinal CSF leak, multiple leaks (including different leak types) can coexist.[3,4]

Imaging is critical in the diagnosis and workup of patients with spontaneous intracranial hypotension. There is no single standard imaging algorithm recommended for patients with spontaneous intracranial hypotension, although various algorithms have been suggested.[5,6] Even among experienced centers, the details of imaging workup are variable. Therefore, this article describes the most frequently used tests based on the authors' experience and current evidence in the literature. In general terms, the radiographic workup of patients with spontaneous intracranial hypotension can be divided into two stages: (1) initial noninvasive imaging intended to support a diagnosis of spontaneous intracranial hypotension and (2) advanced myelographic techniques aimed at precisely localizing and classifying the type of spinal CSF leak.

INITIAL IMAGING

When a clinical diagnosis of spontaneous intracranial hypotension is suspected, imaging of the brain and spine is indicated. Brain imaging is necessary to evaluate for typical intracranial findings of spontaneous intracranial hypotension and to exclude other etiologies for the patient's symptoms. Spine imaging is needed to assess for secondary findings that may suggest an etiology of CSF leak, such as spinal extradural CSF (ie, direct evidence that a leak exists, although it does not necessarily indicate the precise location) or meningeal diverticula (ie, regions of dura that may be prone to leaking or forming CSF-venous fistulas). Several imaging modalities can be used, with relative advantages and disadvantages as summarized in **TABLE 2-1**. The remainder of this article describes the various techniques in more detail. The authors' suggested diagnostic workup for spontaneous intracranial hypotension is summarized in **FIGURE 2-1**.

Brain Imaging

The initial test of choice for suspected spontaneous intracranial hypotension is brain MRI with and without IV gadolinium-based contrast. Brain MRI findings of spontaneous intracranial hypotension include diffuse pachymeningeal or dural enhancement, engorgement of the dural venous sinuses, subdural hematomas or hygromas, superficial siderosis, effacement of the suprasellar cistern, effacement of the prepontine cistern, reduction of the mamillopontine distance, and inferior cerebellar tonsillar ectopia (**CASE 2-1**). The last four of these imaging findings are often collectively referred to as *brain sagging* because of the slumped appearance of the posterior fossa structures caused by CSF volume depletion. Not all of these findings are necessarily present in patients with confirmed spontaneous intracranial hypotension. Indeed, some patients with spontaneous intracranial hypotension have a completely normal brain MRI. The proportion of patients with a normal brain MRI with confirmed spinal CSF leak may be as high as 19%.[7] A scoring system assigning points to some of these imaging findings was shown to predict the probability of finding a CSF leak on myelography, often referred to as the *Bern score*.[8] This scoring system was initially derived from a cohort of patients with spinal extradural CSF (type 1 leaks) and has been validated for other leak types and at other centers (**TABLE 2-2**).[9,10] Some centers have elected to include this scoring system in brain MRI radiology reports.

It is important to tailor brain MRI protocols to optimize evaluation for spontaneous intracranial hypotension while also providing an opportunity to identify other potentially treatable causes of a patient's symptoms. At a minimum, the authors recommend the following sequences:

- **Sagittal three-dimensional (3D) T1-weighted noncontrast: This sagittal view helps assess for brain sagging. Additionally, this sequence allows for the identification of intrinsically T1-hyperintense blood products.**
- **Axial T2-weighted: This sequence may help characterize subdural fluid collections, as well as provide a cursory evaluation of the intracranial vessels (flow voids) to exclude a large aneurysm.**

KEY POINTS

- **Spontaneous intracranial hypotension is characteristically caused by a CSF leak in the spine.**
- **Spinal CSF leak types include dural tears (type 1), leaking meningeal diverticula (type 2), and CSF-venous fistulas (type 3).**
- **Brain MRI with and without IV contrast is the initial test of choice in patients with suspected spontaneous intracranial hypotension.**
- **The Bern score reflects the probability of finding a spinal CSF leak on subsequent myelography.**

- **Axial or 3D T2 fluid-attenuated inversion recovery (FLAIR): This sequence provides an optimal evaluation of subdural collections. It also facilitates evaluation for white matter lesions, such as demyelinating plaques, which could represent a separate etiology for a patient's symptoms.**
- **Axial susceptibility-weighted imaging (SWI): This sequence is particularly helpful in detecting superficial siderosis or other intracranial hemorrhage.**
- **Axial postgadolinium T1-weighted: This sequence is needed to evaluate for dural enhancement and exclude any brain parenchymal enhancing lesions. Various types of postgadolinium sequences exist, each with advantages and disadvantages. For example, 3D turbo spin echo (eg, sampling perfection with application-optimized contrasts using different flip-angle evolutions [SPACE], CUBE, or driven equilibrium radio frequency reset pulse [DRIVE]) sequences are highly sensitive for dural enhancement, whereas 3D gradient echo (GRE) (eg, magnetization-prepared rapid gradient echo [MP-RAGE] or spoiled gradient recalled acquisition [SPGR]) sequences are optimal for the evaluation of the dural venous sinuses.**

Although noncontrast head CT is less sensitive than MRI and, thus, typically not recommended for spontaneous intracranial hypotension evaluation, it can show

TABLE 2-1

Primary Imaging Modalities for Investigating Spontaneous Intracranial Hypotension and Underlying Spinal CSF Leaks

Imaging modality	Major advantages	Limitations	Key questions answered
Brain MRI	Noninvasive; excellent soft-tissue contrast allows detailed assessment of brain sagging, venous engorgement, and dural thickening	Not available in all areas, contraindicated in patients with some metal or electronic implants	Are there cranial imaging findings to support a diagnosis of spontaneous intracranial hypotension?
Brain CT	Noninvasive, widely available	Less sensitive than MRI for subtle brain sagging, venous engorgement, or dural thickening	Are there cranial imaging findings to support a diagnosis of spontaneous intracranial hypotension?
Radioisotope cisternogram[a]	More sensitive than brain MRI for abnormal CSF dynamics suggestive of spontaneous intracranial hypotension	Requires lumbar puncture, radioisotope has a short half-life and is not widely available, generally cannot localize CSF leaks because of low spatial resolution	Are there findings of abnormal CSF flow to support a diagnosis of spontaneous intracranial hypotension?
Spine MRI	Noninvasive, shows the presence or absence of an extradural fluid collection to guide patient positioning on subsequent invasive myelography	Generally cannot localize CSF leaks without intrathecal gadolinium, epidural fat and engorged epidural veins can be mistaken for extradural CSF if fat-suppressed sequences are not performed	Are there spine findings to suggest a specific type of CSF leak?
Conventional CT myelogram[a]	Widely available, shows the presence or absence of an extradural fluid collection in patients who cannot undergo MRI or when MRI is not available	Requires lumbar puncture, poor temporal resolution, diffusion of contrast throughout spinal canal before image acquisition eliminates dense contrast bolus required to fill nerve root sleeve diverticula and opacify associated fistulas	Are there spine findings to suggest a specific type of CSF leak? (Often performed with unrealistic expectation that it will show the type and location of a CSF leak)

CONTINUED ON PAGE 671

some of the manifestations of spontaneous intracranial hypotension and should be considered in areas with less access to MRI or for patients who cannot undergo MRI. CT can show brain sagging when it is severe and accompanied by diffuse hyperostosis of the calvarium; the latter can occur in chronic, untreated cases of spontaneous intracranial hypotension secondary to the loss of expansile force from the underlying brain and CSF that normally fills the intracranial compartment and maintains its intrinsic volume.[11] Subdural hematomas and hygromas can also be seen well on CT and, when occurring in the absence of trauma, should raise suspicion for spontaneous intracranial hypotension.

Spine Imaging

Initial spine imaging in patients with spontaneous intracranial hypotension varies by institutional preference. Available screening imaging includes MRI of the entire spine and conventional CT myelography.

CONTINUED FROM PAGE 670

Imaging modality	Major advantages	Limitations	Key questions answered
Dynamic CT myelogram on energy integrating detector or photon-counting detector scanner[a]	Includes cross-sectional detail, permits imaging of the entire spine	Requires lumbar puncture, higher radiation dose than digital subtraction myelography (though many centers perform a CT scan following the digital subtraction myelogram, resulting in a roughly comparable total radiation dose), lower temporal and spatial resolution than digital subtraction myelography (except photon-counting CT, which rivals resolution of digital subtraction myelography)	What type and where is the CSF leak?
Digital subtraction myelogram[a]	High temporal resolution, high spatial resolution	Requires lumbar puncture, lacks cross-sectional detail, field of view limited	What type and where is the CSF leak?
MR myelogram (with intrathecal gadolinium)[a,b]	High soft-tissue contrast resolution	Requires lumbar puncture, poor temporal resolution reduces sensitivity for localizing most CSF-venous fistulas and essentially all leaks associated with extradural fluid collections	What type and where is the CSF leak?

[a] Although lumbar puncture opening pressure can be measured at the start of this procedure, note that CSF pressure is normal in most patients with spontaneous intracranial hypotension, and only abnormally low pressure (<6 cm H_2O) is diagnostically useful.
[b] Intrathecal administration of gadolinium is unlabeled.

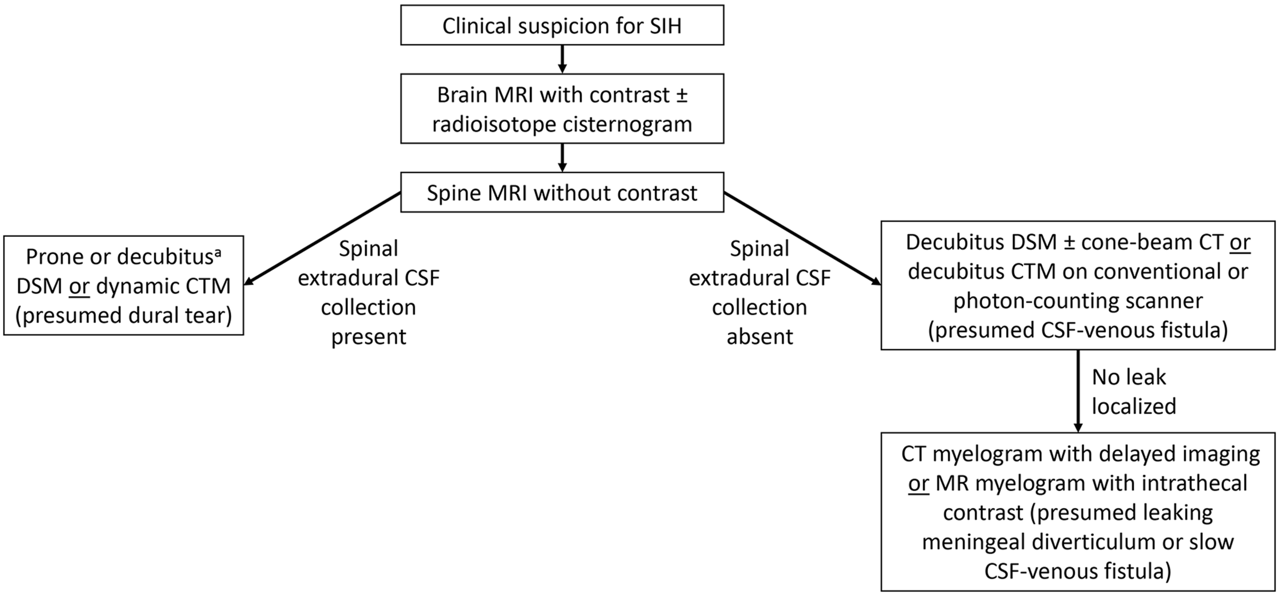
Clinical suspicion for SIH
Brain MRI with contrast ± radioisotope cisternogram
Spine MRI without contrast
Spinal extradural CSF collection present
Prone or decubitus[a] DSM or dynamic CTM (presumed dural tear)
Spinal extradural CSF collection absent
Decubitus DSM ± cone-beam CT or decubitus CTM on conventional or photon-counting scanner (presumed CSF-venous fistula)
No leak localized
CT myelogram with delayed imaging or MR myelogram with intrathecal contrast (presumed leaking meningeal diverticulum or slow CSF-venous fistula)

FIGURE 2-1

Suggested imaging approach for localizing spontaneous spinal CSF leaks.

CTM = CT myelography; DSM = digital subtraction myelography; SIH = spontaneous intracranial hypotension.

[a] Depending on the location of extradural fluid collection.

The most important purpose of screening spine imaging in patients with spontaneous intracranial hypotension is to assess for the presence or absence of extradural CSF within the spinal canal (FIGURE 2-3). Extradural CSF strongly suggests the presence of a dural tear (ie, a fast leak), whereas the absence of extradural CSF in a patient with spontaneous intracranial hypotension implies the presence of a CSF-venous fistula or, less commonly, a laterally leaking meningeal diverticulum (ie, a slow leak). Although the precise location of dural tears is rarely seen on spine MRI, the distribution of extradural CSF can suggest the location of the tear around the perimeter of the spinal canal. For example, a predominantly ventral extradural CSF collection usually indicates a ventral dural tear, whereas a largely dorsal or lateral collection may suggest a posterolateral dural tear. This knowledge can help guide patient positioning for any subsequent myelography. Spine MRI can also detect meningeal diverticula, which are frequently associated with type 2 and type 3 leaks. The presence and size of spinal meningeal diverticula (often called *perineural cysts* even though they are not true cysts) do not always correlate with the diagnosis of spontaneous intracranial hypotension because they are common in asymptomatic individuals.[12] Occasionally, fluid may be seen in the paraspinal musculature, which can provide a clue to the location of a leaking meningeal diverticulum.

Spine MRI protocols should include at least the following sequences when evaluating for possible CSF leak:

- **Axial and sagittal T2-weighted imaging with fat suppression (eg, short tau inversion recovery [STIR]): These sequences are the key sequences to identify extradural CSF. Fat suppression is needed to distinguish fluid from T2-hyperintense epidural fat.**

◆ **High-resolution 3D turbo spin echo T2-weighted imaging with fat suppression: This refers to sequences such as SPACE, CUBE, and DRIVE. These provide thin-section imaging to confirm or exclude suspected extradural CSF collections seen on conventional T2-weighted imaging. Some authors refer to these as "myelographic" sequences, although they do not involve the instillation of any intrathecal contrast material. Many centers also use sequences such as fast imaging employing steady state acquisition (FIESTA) and constructive interference in steady state (CISS), which have even higher resolution but are not purely T2 weighted.**

IV contrast is not usually needed for initial spine imaging. Spine MRI with intrathecal gadolinium is occasionally performed in patients with spontaneous intracranial hypotension but is an unlabeled use and has not been shown to increase the sensitivity for detecting extradural CSF collections compared with heavily T2-weighted imaging without contrast.[13] Intrathecal gadolinium MR myelography may be useful in detecting leaking meningeal diverticula and CSF-venous fistulas, although its yield is likely lower than other techniques.[14-16] It bears repeating that the intrathecal administration of gadolinium is an unlabeled use, although it is safe when done with proper technique and at a low dose of gadolinium.[17]

An alternative to MRI of the spine is conventional CT myelography, which involves intrathecal injection of iodinated contrast under fluoroscopic guidance with a delayed CT scan obtained 10-20 minutes later. Studies have demonstrated that heavily T2-weighted MR myelography has a similar yield for detecting extradural CSF compared with conventional CT myelography.[18] Because the latter requires a minimally invasive injection and ionizing radiation, the authors generally prefer spine MRI over CT myelography in the initial screening for extradural CSF.

Radioisotope Cisternography

Radioisotope (or radionuclide) cisternography involves intrathecal injection of a radioisotope such as indium-111 disodium pentetate, with subsequent planar imaging to assess migration of the injected radiotracer up the spinal canal and throughout the calvarium. Patients with spontaneous intracranial hypotension have a slower than normal ascent of radiotracer.[5] Incomplete ascent of radiotracer over the cerebral convexities by 24 hours is considered abnormal and suggestive of a spinal CSF leak (of any type). Early visualization of radiotracer in the kidneys or bladder (before 4 hours) usually reflects a secondary finding of CSF-venous fistula, although this also can be seen with an inadvertent venous injection of radiotracer. Although this test typically cannot localize CSF leaks, it may be useful to determine whether a spinal CSF leak is present, particularly in patients with a normal brain MRI but lingering clinical suspicion for spontaneous intracranial hypotension.

ADVANCED MYELOGRAPHY

After determining whether extradural CSF is present in the spine, advanced myelographic techniques are necessary to pinpoint the site of a CSF leak. The two most common myelographic tests currently used are digital subtraction myelography and dynamic CT myelography.[5] Both of these tests include one key component in identifying most CSF leaks: Imaging is performed immediately after injection of intrathecal contrast. CSF leaks are difficult to localize on myelography if imaging is delayed by even a few minutes after

KEY POINTS

- **The main purpose of spine MRI in patients with spontaneous intracranial hypotension is to assess for the presence of extradural CSF collections.**

- **T2-weighted fat-suppressed MRI is particularly important in distinguishing extradural CSF from epidural fat.**

- **The most commonly used advanced myelographic techniques to pinpoint the site of a CSF leak are digital subtraction myelography and dynamic CT myelography. Digital subtraction myelography has the best spatial and temporal resolution, but dynamic CT myelography provides cross-sectional detail. Photon-counting CT rivals digital subtraction myelography in spatial resolution.**

- **Digital subtraction myelography and dynamic CT myelography are performed with imaging rapidly after intrathecal contrast injection in patients with spontaneous intracranial hypotension.**

- **Patients with extradural CSF on spine MRI usually have a dural tear (type 1a or 1b leak).**

contrast injection because contrast quickly equilibrates between the subarachnoid space and other compartments (epidural space or venous system). Thus, contrast leaking through a dural tear or CSF-venous fistula is extremely difficult to see on delayed imaging. One exception to this is a leaking meningeal diverticulum (type 2 leak), which is often better localized on delayed CT myelography[5]; this is because leaks from meningeal diverticula are generally slower leaks, and delayed imaging helps by providing time for contrast to accumulate around the diverticulum. On rare occasions, spine MRI (particularly intrathecal gadolinium MR myelography) is sufficient to localize type 2 leaks.[15,16]

CASE 2-1

A 60-year-old woman was evaluated for 1 month of headaches that appeared when she arose from bed each morning and were relieved with recumbency even without sleep. Headaches were also triggered or exacerbated by cough, strain, or bending forward. Although she recalled an abrupt onset of these headaches, she had no history of trauma or other inciting events. Brain MRI without and with IV gadolinium contrast (FIGURE 2-2) showed signs of spontaneous intracranial hypotension. Spine MRI without IV contrast showed multiple meningeal diverticula but no extradural CSF or other abnormalities. Based on these findings, a spontaneous CSF-venous fistula was thought to be the most likely cause of CSF leakage. Decubitus CT myelography showed a right T8 CSF-venous fistula.

COMMENT

A new daily headache that worsens with upright posture, with Valsalva maneuvers, and later in the day (ie, "second-half-of-the-day headache") is highly suggestive of spontaneous intracranial hypotension. The first step in evaluating a patient with suspected spontaneous intracranial hypotension should be brain MRI without and with gadolinium contrast to determine if brain sagging, pachymeningeal enhancement, venous engorgement, and subdural fluid collections are present. The possibility of finding an underlying spinal CSF leak increases with the number of intracranial stigmata of spontaneous intracranial hypotension that are seen on brain MRI.

Digital Subtraction Myelography

Digital subtraction myelography refers to a fluoroscopic myelogram typically performed in a high-quality interventional imaging suite, similar to those used for neuroangiography.[19] Such machines often have biplane imaging capabilities, allowing for simultaneous acquisition of an anteroposterior and a lateral projection. A lumbar puncture is performed in the interventional suite, and the imaging detectors are centered over the spinal region of interest. Multiple sets of acquisitions (at least two) may be needed to image the entire spine. Once the imaging detectors are correctly centered over the spinal region of interest, iodinated contrast material is injected under continuous fluoroscopic imaging

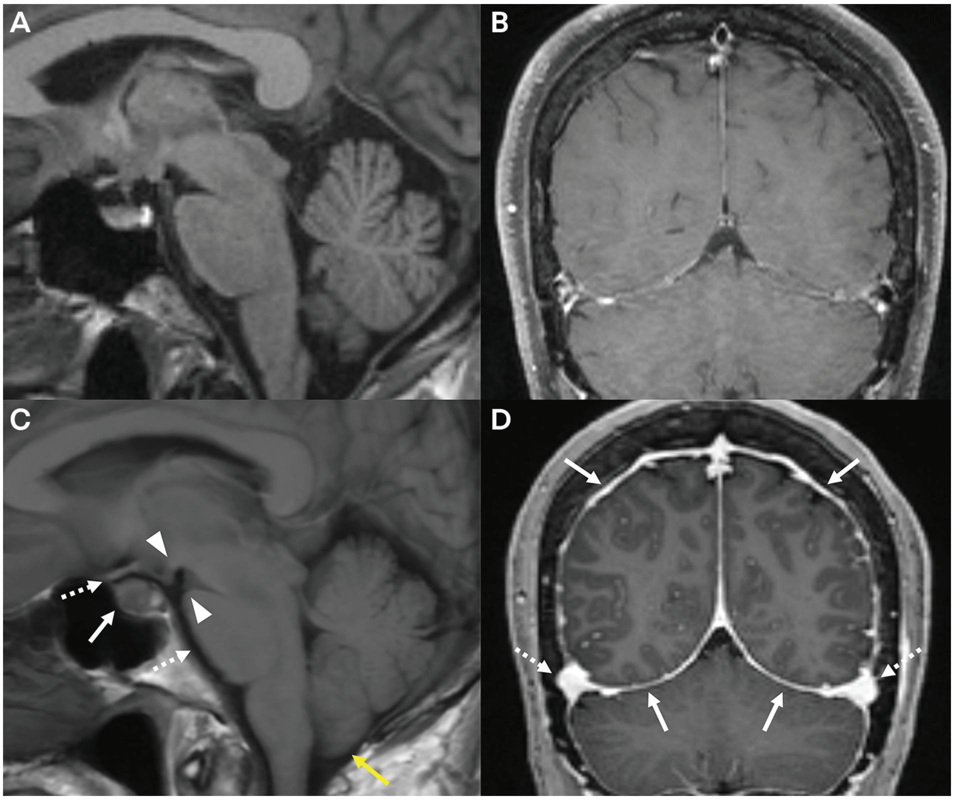

FIGURE 2-2

Imaging findings from the patient in CASE 2-1. Brain MRI 2 years before (*A*, *B*) and 1 month after (*C*, *D*) onset of daily headaches with orthostatic and Valsalva worsening. T1-weighted sagittal precontrast (*A*) and coronal postcontrast (*B*) images, which were obtained for routine follow-up of a meningioma, show a normal appearance of the posterior fossa structures (*A*) and normal nonenhancing dural (*B*). Sagittal precontrast T1-weighted image (*C*) shows new engorgement of the pituitary gland (*solid arrow*), effacement of the suprasellar and prepontine cisterns (*dashed arrows*), reduction of the mamillopontine distance (*arrowheads*), and new mild inferior cerebellar tonsillar descent (*yellow arrow*). Coronal postcontrast T1-weighted image (*D*) shows new diffuse pachymeningeal (dural) gadolinium enhancement (*solid arrows*), as well as new engorgement of the transverse sinuses (*dashed arrows*).

with a frame rate of 1 to 2 frames per second. Digital subtraction is applied to remove bone and other dense structures from the image. Generally, contrast with a high iodine concentration (300 mg/mL) is preferred to maximize contrast density.

The primary advantage of digital subtraction myelography is its high temporal resolution. Images are acquired rapidly at 1 to 2 frames per second, allowing for real-time visualization of CSF leaks. Another major advantage is high spatial resolution, allowing for precise discrimination of tiny adjacent structures. The main disadvantage of digital subtraction myelography is that it lacks cross-sectional detail. Therefore, CSF leaks superimposed over contrast-opacified structures such as meningeal diverticula can be missed. Most machines are capable of performing a cone beam CT, which generally has a lower quality than a conventional CT scan but can be a useful adjunct to digital subtraction myelography.[20]

Dynamic CT Myelography

Dynamic CT myelography is a CT-based myelogram that is usually performed using a high-resolution detector CT scanner.[21,22] As opposed to a conventional CT myelogram, dynamic CT myelography involves multiple scans of the spine in rapid succession during active intrathecal injection of iodinated contrast. For convenience and safety, this usually requires performing the lumbar puncture on the CT scanner table. After CT-guided lumbar puncture, two to six scans of the spine are performed while contrast is injected. Multiple scans are needed to confer some degree of temporal resolution to the examination. As with digital subtraction myelography, a high-density contrast agent containing iohexol at a concentration of 300 mg/mL is usually used, although some providers prefer a concentration of 240 mg/mL to mitigate beam-hardening artifact from the dense intrathecal contrast.

The main advantage of dynamic CT myelography is that, unlike digital subtraction myelography, it intrinsically has cross-sectional detail. Furthermore, CT exquisitely characterizes complex anatomic structures, allowing for

TABLE 2-2 **Brain MRI Scoring System to Determine the Probability of Finding a Spinal CSF Leak (Bern Score)[a]**

Major criteria (2 points each)

- **Pachymeningeal enhancement**
- **Engorgement of dural venous sinuses**
- **Suprasellar cistern ≤4 mm**

Minor criteria (1 point each)

- **Subdural fluid collections**
- **Prepontine cistern ≤5 mm**
- **Mamillopontine distance ≤6.5 mm**

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[a] Low probability (0-2 points), intermediate probability (3-4 points), high probability (5-9 points).

identification of bone spicules and other lesions that may be diagnostically important.[23] Dynamic CT myelography also permits imaging of the entire spine because CT is not limited by the size of the imaging detector like digital subtraction myelography. Disadvantages of dynamic CT myelography include its relatively higher radiation dose, decreased spatial resolution compared with digital subtraction myelography, and lower temporal resolution.[24] The sensitivity of dynamic CT myelography can be enhanced with use of dual-energy techniques to improve iodine conspicuity.

EXTRADURAL CSF PRESENT ON SPINE IMAGING

If patients have extradural CSF within the spinal canal found on initial spine imaging, the most likely etiology for their CSF leak is a dural tear. Dural tears are usually ventral (type 1a) (**FIGURE 2-4** and **FIGURE 2-5**) or posterolateral (type 1b) (**FIGURE 2-6**). Ventral dural tears are frequently associated with an osseous spicule penetrating the otherwise normal dura, whereas posterolateral dural tears typically occur in patients with connective tissue disorders that cause weakened dura. Sometimes, posterolateral dural tears can be associated with an osseous spicule arising from the posterior elements.

Dural Tears

Localization of dural tears can be accomplished with either digital subtraction myelography or dynamic CT myelography. If a ventral dural tear is suspected, patients should be moved to a prone position.[25,26] If a posterolateral dural tear is suspected, patients should be in the left or right decubitus position (typically, left versus right is determined based on which side harbors a greater amount

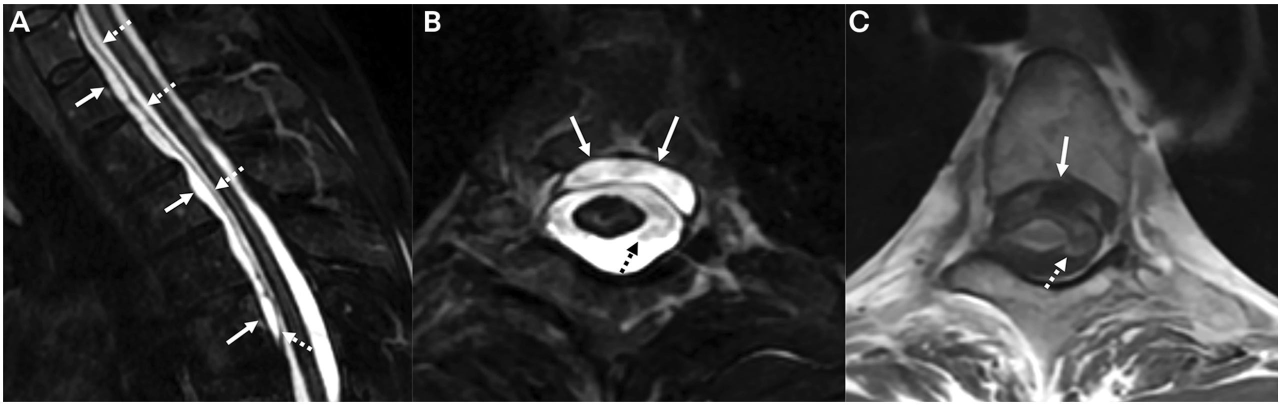

FIGURE 2-3
Spine MRI from a 61-year-old woman shows a ventral extradural CSF collection, which strongly suggests the presence of a dural tear but does not identify the precise spinal level of the leak. Sagittal high-resolution T2-weighted CUBE image (*A*) with fat suppression shows a ventral extradural CSF collection spanning multiple upper thoracic and cervical levels (*A*, *arrows*), clearly separated from the thecal sac by the ventral dura (*A*, *dashed arrows*). High-resolution imaging can be helpful in clearly delineating the dura separating intrathecal from extrathecal CSF. Axial T2-weighted fat-suppressed (*B*) and T1-weighted (*C*) images through the middle of the extradural collection show the expected T2-hyperintense (*B*, *solid arrows*) and T1-hypointense (*C*, *solid arrow*) appearance of the extradural CSF. Flow artifact (*B*, *C*, *dashed arrows*) is a common finding related to normal CSF pulsation, which should not be mistaken for an alternative abnormality.

of extradural CSF or the most prominent meningeal diverticula on previous spine imaging).[27] Ultimately, choosing between digital subtraction myelography or dynamic CT myelography for localization of dural tears depends on many factors, including availability of resources and radiologist preference. Importantly, if a ventral leak is suspected in the upper thoracic or low cervical spine, leak localization with digital subtraction myelography may be challenging because the shoulders degrade the quality of a lateral projection in this region.[28] Dynamic CT myelography may be preferred for these patients.

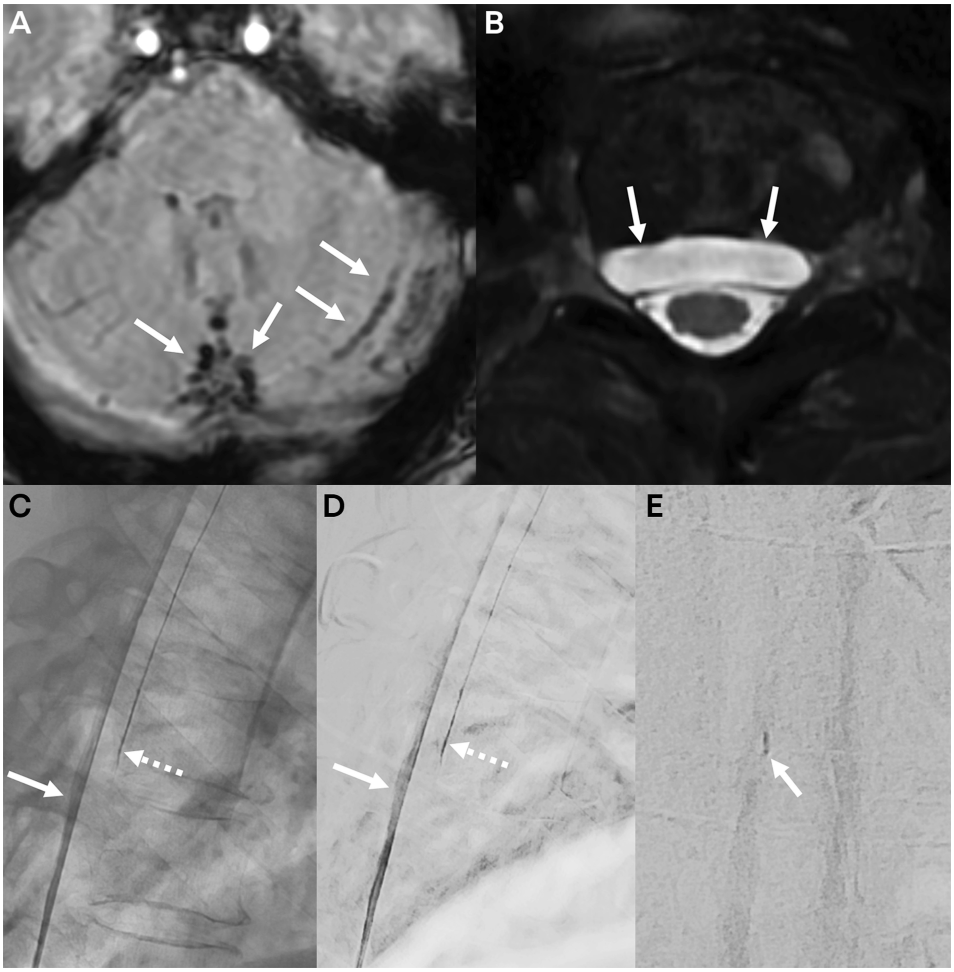

FIGURE 2-4

Ventral dural tear (type 1a CSF leak) diagnosed on a prone digital subtraction myelogram in a 50-year-old man with years of orthostatic headaches. Axial susceptibility-weighted image (SWI) (*A*) from his brain MRI shows multiple areas of hypointense signal along the cerebellar folia and vermis (*A*, *arrows*), consistent with superficial siderosis. Axial T2-weighted and fat-saturated image (*B*) from his spine MRI, centered at T6, shows a large ventral extradural CSF collection (*B*, *arrows*), which extended over multiple spinal levels. Images from subsequent prone digital subtraction myelogram (*C*, lateral unsubtracted image; *D*, lateral subtracted image; and *E*, anteroposterior subtracted image) show a ventral dural tear at T7-T8, where there is a clear split between intrathecal contrast (*C*, *D*, *solid arrows*) and extradural contrast (*C*, *D*, *dashed arrows*). The anteroposterior image shows that the precise dural tear is slightly to the left of the midline (*E*, *solid arrow*).

The characteristic finding on myelography in a patient with a dural tear is a split contrast column, wherein there is direct visualization of a column of contrast leaking into the epidural space that is distinct from intrathecal contrast (FIGURES 2-4, 2-5, and 2-6). Dynamic imaging is necessary to identify precisely where this split occurs because contrast ascends from the lumbar spine to the cervical spine. Delayed myelography is usually not capable of localizing such dural tears (FIGURE 2-5C).

EXTRADURAL CSF ABSENT ON SPINE IMAGING

In patients with spontaneous intracranial hypotension but no extradural CSF on initial spine imaging, who constitute the majority, the most common etiology for CSF leak is a CSF-venous fistula.[29] Less commonly, these patients may have a leaking meningeal diverticulum. Leaking diverticula are sometimes evident on spine MRI or delayed CT myelography (FIGURE 2-7). CSF-venous fistulas are commonly associated with meningeal diverticula, which may be seen on spine imaging, but the actual CSF-venous fistula is never visible on spine MRI and only rarely visible on conventional CT myelography.

CSF-Venous Fistulas

Both digital subtraction myelography and dynamic CT myelography can be used to precisely localize CSF-venous fistulas. All these patients should be studied while they are in the lateral decubitus position.[9,30,31] Because there is no reliable way to predict whether the leak is on the right or left side, a myelogram should be obtained in both decubitus positions. Depending on radiologist preference and patient-specific factors, this may require a 2-day myelogram.[32] However,

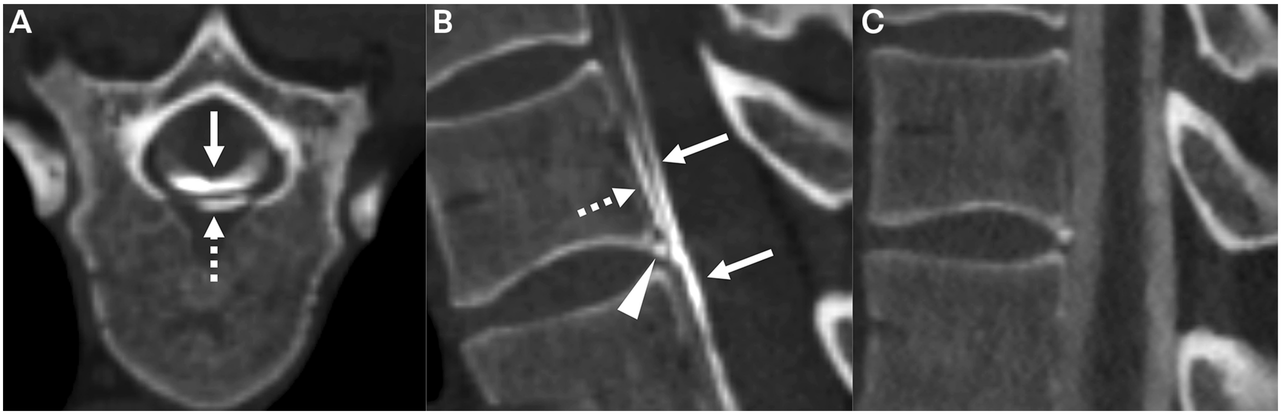

FIGURE 2-5

Ventral dural tear (type 1a CSF leak) diagnosed with prone dynamic CT myelography in a 38-year-old woman with progressive orthostatic headaches. Spine MRI (*not shown*) showed ventral extradural CSF over multiple spinal levels. Axial (*A*) and sagittal (*B*) images from a prone dynamic CT myelogram show a ventral leak at T11-T12 with a clear split of intrathecal contrast (*A*, *B*, *solid arrows*) and extradural (*A*, *B*, *dashed arrows*) contrast. A tiny bone spicule arising from the T11-T12 interspace (*B*, *arrowhead*) was the likely cause of the leak. Sagittal reconstruction from a 10-minute delayed scan (*C*) no longer shows the precise leak site, with a homogenous appearance of the intrathecal and extradural contrast. Immediate scanning during intrathecal contrast injection is necessary to localize dural tears.

same-day bilateral decubitus CT myelography techniques have been described.[32] The main challenge in identifying CSF-venous fistulas at myelography is the transient nature of opacification of draining veins.[33] For this reason, imaging must be performed immediately after injecting contrast. Digital subtraction myelography has the advantage of very high temporal resolution, which is excellent for identifying veins that may opacify for only a short time. Dynamic

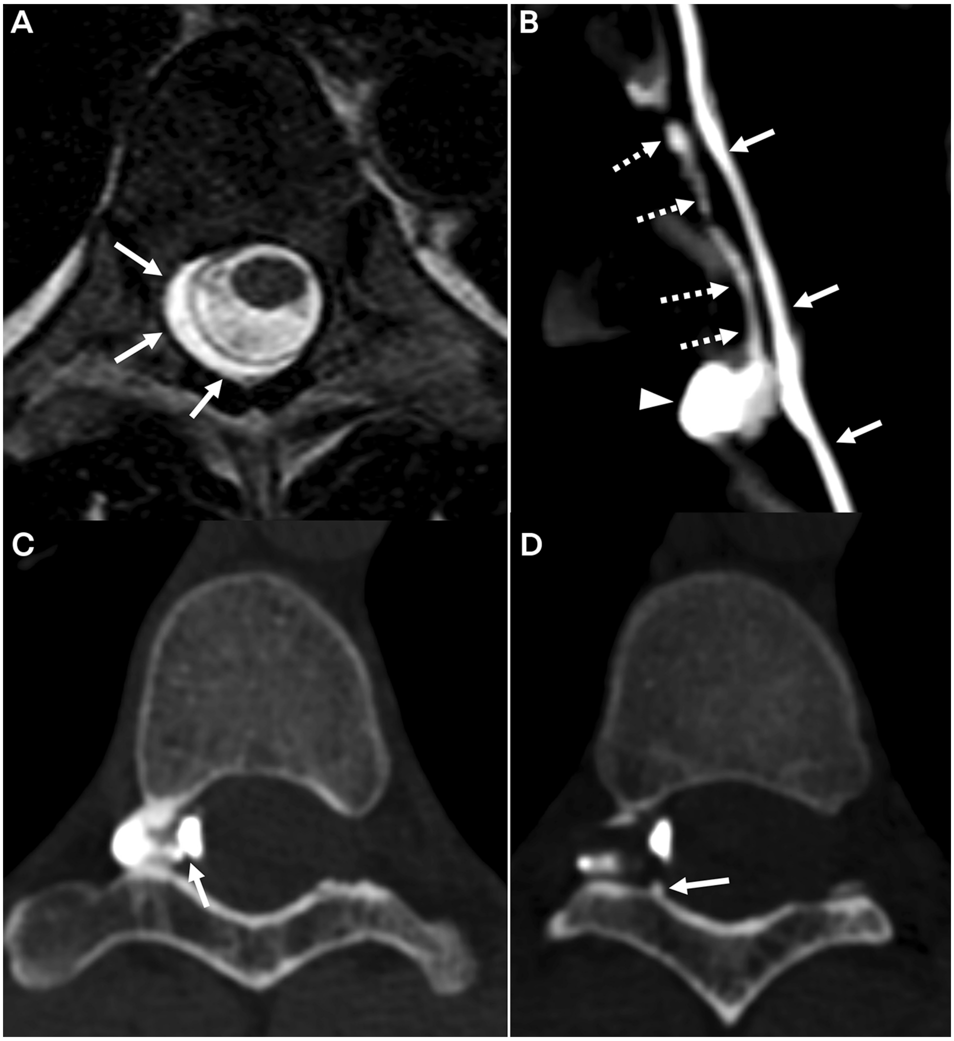

FIGURE 2-6

Posterolateral dural tear (type 1b CSF leak) diagnosed on decubitus dynamic CT myelography in a 30-year-old woman with acute-onset orthostatic headaches. *A*, T2-weighted MRI shows extradural CSF in the right lateral and dorsal epidural space (*arrows*), which was present over multiple spinal levels. Based on this finding, a right-sided leak was suspected. *B*, Coronal image from right lateral decubitus dynamic CT myelogram shows a posterolateral CSF leak at T9 on the right with a clear split of intrathecal contrast (*solid arrows*) and extradural contrast (*dashed arrows*). A prominent diverticulum is present at this level (*arrowhead*), which represents arachnoid protruding through a posterolateral dural defect. *C*, Axial image from the myelogram at T9 shows the precise site of the dural tear at approximately the 8-o'clock position of the thecal sac near the nerve root sleeve (*arrow*). *D*, An adjacent image from the myelogram shows a tiny osseous spicule arising from the T9 lamina (*arrow*), which was thought to be the cause of the leak in this patient.

CT myelography has lower temporal resolution but has the advantage of cross-sectional detail, allowing it to identify opacified veins that may be missed on digital subtraction myelography because of overlapping structures. As with dural tears, the choice between digital subtraction myelography and dynamic CT myelography often comes down to institutional resource availability and radiologist preference. Conspicuity of CSF-venous fistulas can be enhanced with certain breathing techniques, including inspiratory phase imaging and resisted inspiration.[34-36]

On digital subtraction myelography, the characteristic finding for a CSF-venous fistula is an opacifying tubular or curvilinear structure that rapidly washes away (FIGURE 2-8A and 2-8B). Cone beam CT, which involves cross-sectional imaging in a fluoroscopy suite using a rotating cone-shaped x-ray source, can be performed during digital subtraction myelography to provide additional information (FIGURE 2-8C and 2-8D), although the image quality is not as exquisite as with actual CT scanners. On dynamic CT myelography, the characteristic finding is contrast opacification of branching, tubular structures representing veins (FIGURE 2-9). Contrast may fill the internal vertebral venous plexus immediately adjacent to the thecal sac, the paraspinal segmental vein, dorsal muscular venous branches, the intercostal vein, and the basivertebral vein.[37] The same veins are seen on digital subtraction myelography, but they are typically identified based on their temporal characteristics rather than anatomic location.

KEY POINTS

- **Digital subtraction myelography or dynamic CT myelography can be performed with the patient in the prone or decubitus position depending on the suspected location of the dural tear.**
- **The characteristic myelographic finding in patients with dural tears is a split contrast bolus.**
- **Patients without extradural CSF on spine MRI usually have a CSF-venous fistula, which is more common than a leaking meningeal diverticulum.**
- **Digital subtraction myelography or dynamic CT myelography should be performed with the patient in the decubitus position to assess for CSF-venous fistulas.**
- **Imaging findings for CSF-venous fistulas include a transiently opacifying vein adjacent to the spinal canal.**

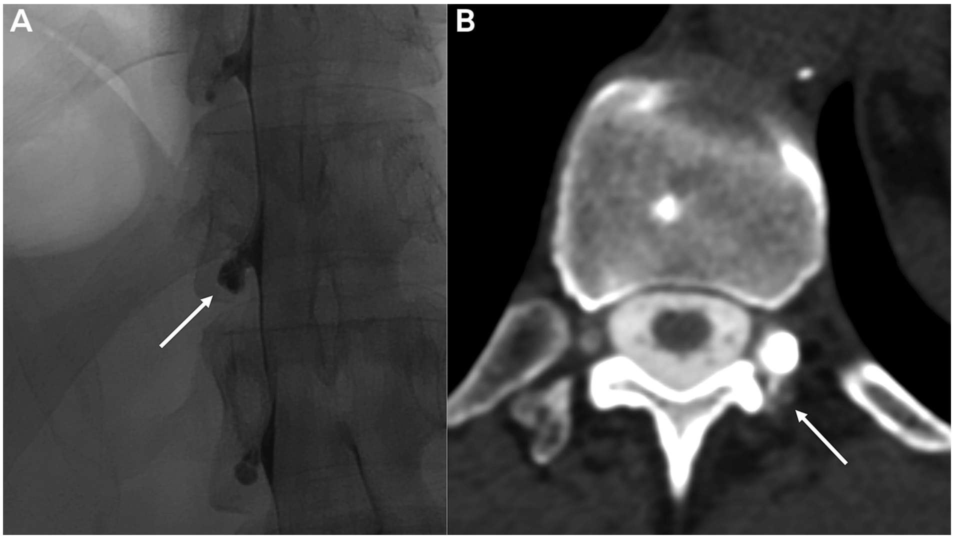

FIGURE 2-7
Leaking meningeal diverticulum (type 2 CSF leak) diagnosed on delayed CT myelography in a 66-year-old woman with several years of orthostatic headaches. The patient's spine MRI was negative for extradural CSF, so decubitus digital subtraction myelography was pursued next. *A*, A representative image from her left decubitus digital subtraction myelogram shows the normal appearance of a left T12 meningeal diverticulum (*arrow*) with no indication of a CSF-venous fistula. *B*, A delayed CT myelogram obtained 30 minutes later shows hazy contrast posterior to the left T12 diverticulum (*arrow*) compatible with a leaking meningeal diverticulum. Type 2 leaks are often best seen on delayed imaging performed at least 30 minutes after intrathecal injection of contrast.

The majority of CSF-venous fistulas occur in the thoracic spine.[9] CSF-venous fistulas can rarely occur in the cervical or lumbar spine, as well as the sacrum.[38] If the initial myelographic workup does not localize a CSF-venous fistula and these portions of the spine were not imaged, one should consider dedicated myelography to assess the parts of the spine that were not initially studied.

Diagnosis of CSF-venous fistulas remains an actively studied and advancing topic, with various techniques used to maximize myelographic sensitivity. One promising area of research is photon-counting CT. Photon-counting CT scanners are a next-generation technology that uses a direct x-ray detector

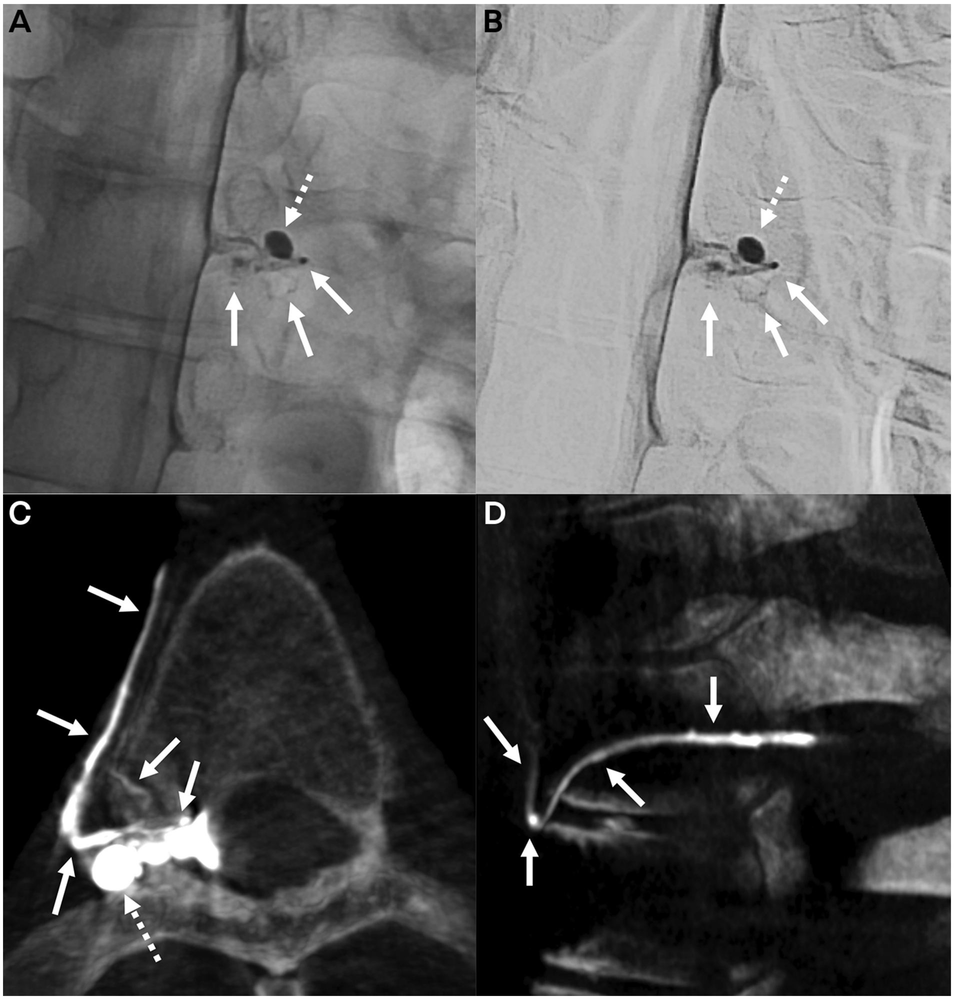

FIGURE 2-8

CSF-venous fistula (type 3 CSF leak) diagnosed on decubitus digital subtraction myelography supplemented with cone-beam CT myelography in a 42-year-old man with orthostatic headaches. Spine MRI was negative for any extradural CSF, whereas brain MRI showed diffuse pachymeningeal enhancement and brain sagging (*not shown*). Unsubtracted (*A*) and subtracted (*B*) images from his right lateral decubitus digital subtraction myelogram show opacification of multiple veins (*A*, *B*, *solid arrows*) surrounding a right T7 meningeal diverticulum (*A*, *B*, *dashed arrows*), compatible with a CSF-venous fistula. Axial (*C*) and sagittal (*D*) images from a cone-beam CT obtained during active intrathecal contrast injection show opacification of a complex network of paraspinal veins (*C*, *D*, *arrows*), clearly separate from the meningeal diverticulum (*C*, *dashed arrow*).

rather than conversion of x-ray energy to light and subsequent light detection. This results in better spatial resolution, faster scanning speeds, and the ability to optimize the CT attenuation (brightness) of iodinated contrast material. One 2023 study showed that decubitus dynamic CT myelography using a photon-counting CT scanner was capable of detecting subtle CSF-venous fistulas missed on both digital subtraction myelography and conventional dynamic CT myelography (**FIGURE 2-10**).[39] Photon-counting CT myelography has also been shown to have a high diagnostic yield for CSF-venous fistula detection.[40] Early evidence suggests it may be advantageous also for localizing dural tears.[41]

By using the algorithm illustrated in **FIGURE 2-1**, most CSF leaks can be localized. It is important to note, however, that there is a subset of patients with spontaneous intracranial hypotension in whom a leak cannot be found despite thorough myelographic evaluation with optimal imaging techniques. In some patients, particularly those with CSF-venous fistulas, this is likely because their leak is intermittent. Repeat myelography can be helpful for these patients if clinically appropriate. In the experience of the authors, CSF-venous fistulas have been localized in several patients after only multiple high-quality myelograms. In other patients, a radiographically subtle or occult CSF leak is suspected.

Leaking Meningeal Diverticula

Leaking diverticula, like CSF-venous fistulas, require decubitus positioning for myelography. The main difference is that leaking diverticula do not always immediately opacify on imaging and may be better detected on delayed CT myelography. The typical imaging finding of a leaking diverticulum is ill-defined

KEY POINTS

- **Photon-counting CT is a promising technologic advancement that aids in the detection of some otherwise missed CSF leaks.**

- **If the initial myelographic workup is negative but the clinical suspicion for spontaneous intracranial hypotension is high, repeat myelography is reasonable.**

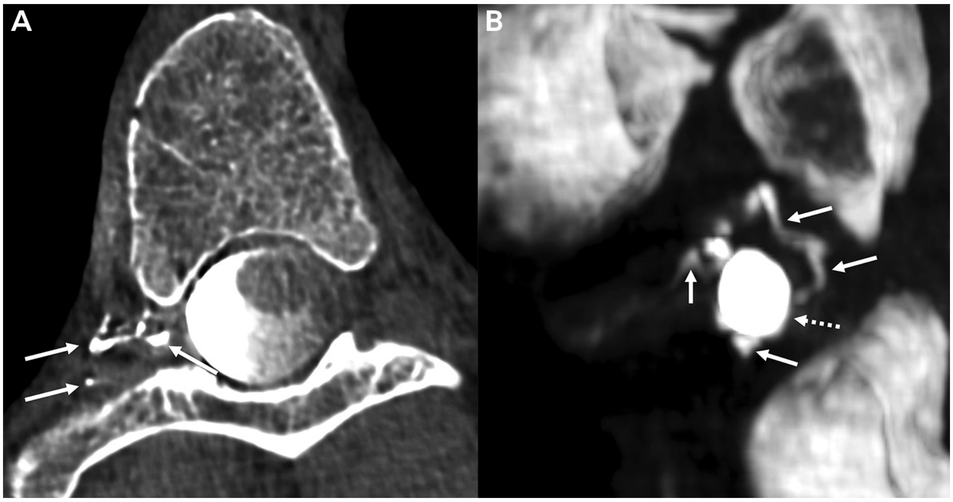

FIGURE 2-9

CSF-venous fistula (type 3 CSF leak) diagnosed with photon-counting CT myelography in a 50-year-old woman with tinnitus and orthostatic headaches. Axial (*A*) and sagittal (*B*) images from a right lateral decubitus dynamic photon-counting myelogram, reconstructed at 0.2-mm slice thickness, exquisitely delineate tiny veins (*A*, *B*, *arrows*) around a right T6 meningeal diverticulum (*B*, *dashed arrow*), compatible with a right T6 CSF-venous fistula. Decubitus CT myelography is a convenient and effective technique for CSF-venous fistula localization, with photon-counting CT scanners providing some benefits over conventional energy–integrating detector scanners.

fluid or contrast adjacent to the diverticulum (FIGURE 2-7). In the experience of the authors, these leaks are far less common than CSF-venous fistulas. Options to assess for leaking diverticula include delayed decubitus CT myelography at least 30 minutes after contrast injection and intrathecal unlabeled gadolinium MR myelography (unlabeled use, with imaging also occurring at least 30 minutes after gadolinium injection).[16] The latter may also sometimes pick up slow or intermittently draining CSF-venous fistulas (FIGURE 2-11).

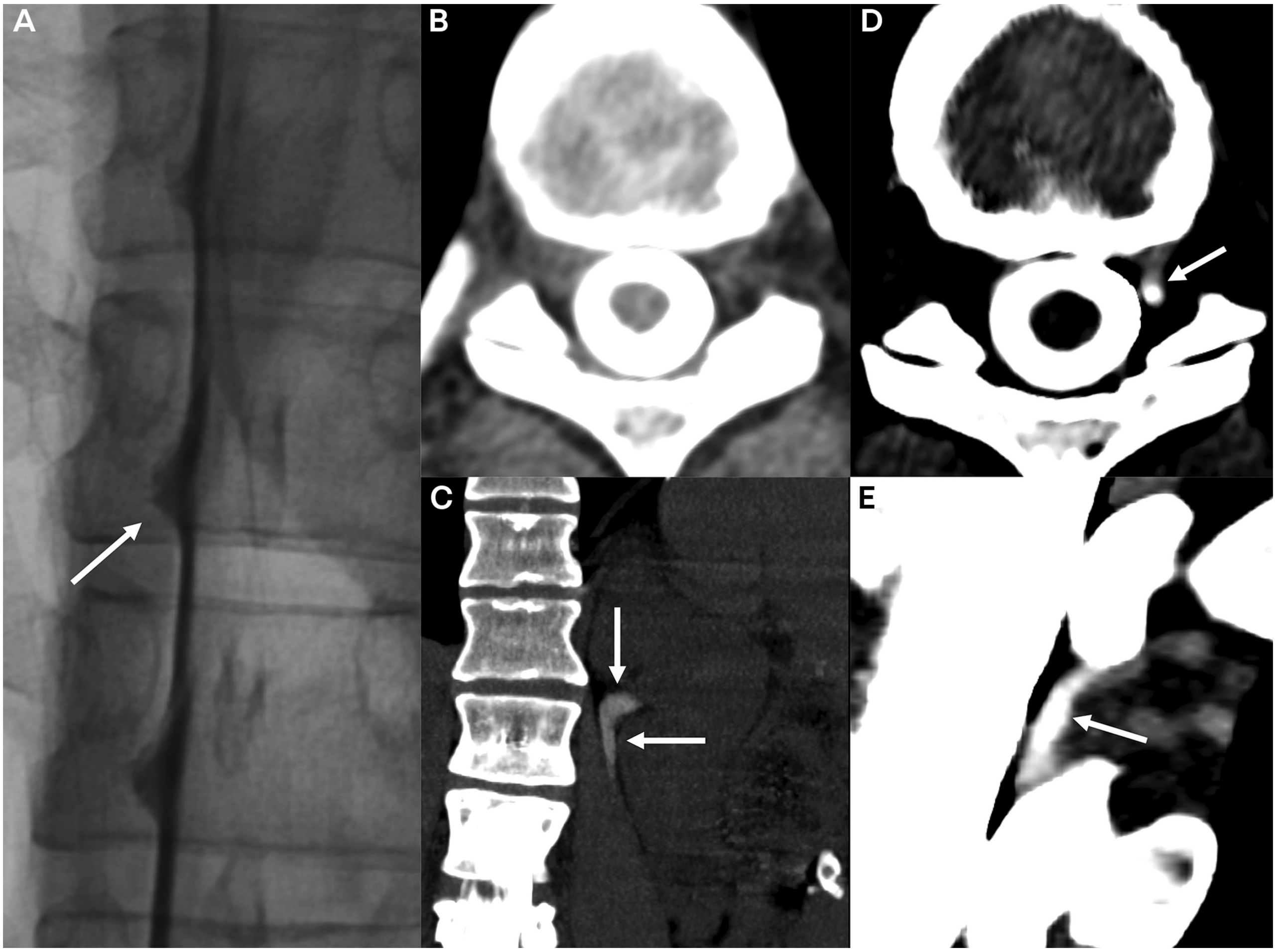

FIGURE 2-10

CSF-venous fistula (type 3 CSF leak) diagnosed with photon-counting CT myelography after a negative digital subtraction myelogram in a 39-year-old woman with years of orthostatic headaches but normal brain MRI. Unsubtracted image from her left decubitus digital subtraction myelogram (*A*) shows the normal appearance of the left T9 nerve root sleeve with no indication of a CSF-venous fistula (*A, arrow*). Delayed axial (*B*) and coronal (*C*) images from a left decubitus CT myelogram obtained 30 minutes after the digital subtraction myelogram again show no CSF-venous fistula at T9 (*B*), although there is contrast excretion in the renal collecting systems suggestive of active CSF leakage into the systemic circulation via a CSF-venous fistula (*C, arrows*). Finally, left decubitus photon-counting CT myelography was performed. Axial (*D*) and coronal (*E*) images from the photon-counting CT myelogram show a clear CSF-venous fistula (*D, E, arrows*) involving the ventral internal vertebral venous plexus. The most subtle CSF-venous fistulas are often in this location and require highly sensitive techniques for detection.

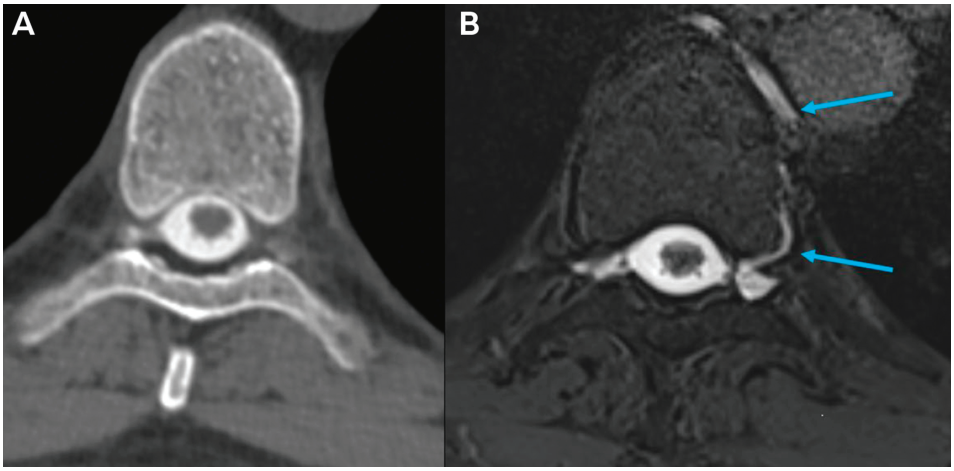

FIGURE 2-11

CSF-venous fistula identified on intrathecal gadolinium (unlabeled use) MR myelography. *A*, Conventional CT myelogram at T7-T8 shows no evidence of CSF-venous fistula. *B*, Subsequent T1-weighted image from intrathecal gadolinium MR myelogram shows contrast in the left T7 paraspinal segmental vein (*arrows*) compatible with a CSF-venous fistula.

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CONCLUSION

Medical knowledge and imaging techniques of spontaneous intracranial hypotension and spinal CSF leaks have improved considerably in recent years. Practicing neurologists should be aware of the different imaging available to help diagnose and localize CSF leaks, as well as the order in which these tests should be performed. Workup should begin with a brain MRI with contrast and imaging of the entire spine, either with spine MRI (preferred) or conventional CT myelography.

If extradural CSF is present on initial spine imaging, a dural tear should be suspected and a digital subtraction myelogram or dynamic CT myelogram should be performed. Optimal patient positioning for this myelogram may be prone or decubitus, depending on the distribution of extradural CSF and the presence of suspicious meningeal diverticula. When extradural CSF is absent, a CSF-venous fistula should be suspected. Digital subtraction myelography and dynamic CT myelography are currently the best tests in these cases, particularly with patients in the decubitus position. Finally, when extradural CSF is absent but a CSF-venous fistula is not found on decubitus digital subtraction myelography or dynamic CT myelography, delayed CT myelography or intrathecal gadolinium MR myelography may add value in assessing for a leaking meningeal diverticulum.

As research in this field progresses, the authors hope that more sensitive and less invasive techniques will be developed to help these patients.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Treatment of Spinal CSF Leaks and Fistulas

By Narayan R. Kissoon, MD; Thien J. Huynh, MD

ABSTRACT

OBJECTIVE: The options for treatment of spontaneous spinal CSF leaks and CSF-venous fistulas have expanded in recent years, and this article reviews the current treatments available, factors that affect treatment outcomes, and an algorithmic approach to treatment.

LATEST DEVELOPMENTS: Until recently, treatments for spontaneous intracranial hypotension consisted of supportive care, epidural blood patching, and when the site of CSF leakage was known, surgical repair. CSF-venous fistulas are now known to be common causes of CSF hypotension and are rarely cured by epidural blood patching. Better visualization of CSF-venous fistulas and the novel treatment of CSF-venous fistulas with transvenous embolization have expanded the arsenal of treatment options for spontaneous intracranial hypotension.

ESSENTIAL POINTS: Clinical outcomes improve with timely treatment of spinal CSF leaks and CSF-venous fistulas. Radiographic features direct treatment, which includes epidural blood patching, transvenous embolization, and surgical correction. CSF-venous fistulas respond poorly to epidural blood patching but can respond favorably to surgical obliteration or transvenous embolization.

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE: Drs Kissoon and Huynh discuss the unlabeled use of fibrin glue in epidural blood patches and a permanent embolic agent for the treatment of CSF leaks.

INTRODUCTION

The syndrome termed *aliquorrhea*, now commonly known as *spontaneous intracranial hypotension*, was described as early as 1938 in association with very low lumbar puncture opening pressure.[1] Later, it was described as being similar to postdural puncture headache.[2-4] Treatment options were limited to supportive measures until the epidural blood patch was first reported by Gormley in 1960 as a treatment for postdural puncture headache.[5] In the 1990s, with the advent of MRI, the radiographic features of spontaneous intracranial hypotension were better characterized, and varied presentations of the disorder were recognized. Clinical outcomes of epidural blood patches were not as favorable in patients with spontaneous intracranial hypotension when compared with those observed in patients with postdural puncture headache.[4] Until the discovery of CSF-venous fistulas as a cause of spontaneous intracranial hypotension in 2014 and the use of transvenous embolization to treat them starting in 2020, treatment options for patients with spontaneous intracranial hypotension refractory to epidural blood patches were limited to invasive surgery and dependent on confident localization of the spinal CSF leak.[6,7] Although clinical decision-making about treatment continues to rely on radiographic features and localization, the treatment options now include epidural blood patching with different approaches (eg, interlaminar, transforaminal) and injectates (eg, autologous blood, fibrin), transvenous embolization, and surgical correction (eg, surgical repair, spinal nerve root ligation, spinal nerve root stripping) (FIGURE 3-1). This article reviews the current treatment options available for patients with spontaneous intracranial hypotension, factors that affect treatment outcomes, and an algorithm to guide treatment. For discussion of the diagnosis of spontaneous intracranial hypotension, refer to the article “Clinical Features and Diagnosis of Spontaneous Intracranial Hypotension” by Jill C. Rau, MD, PhD, and Jeremy K. Cutsforth-Gregory, MD, FAAN,[8] in this issue of *Continuum*.

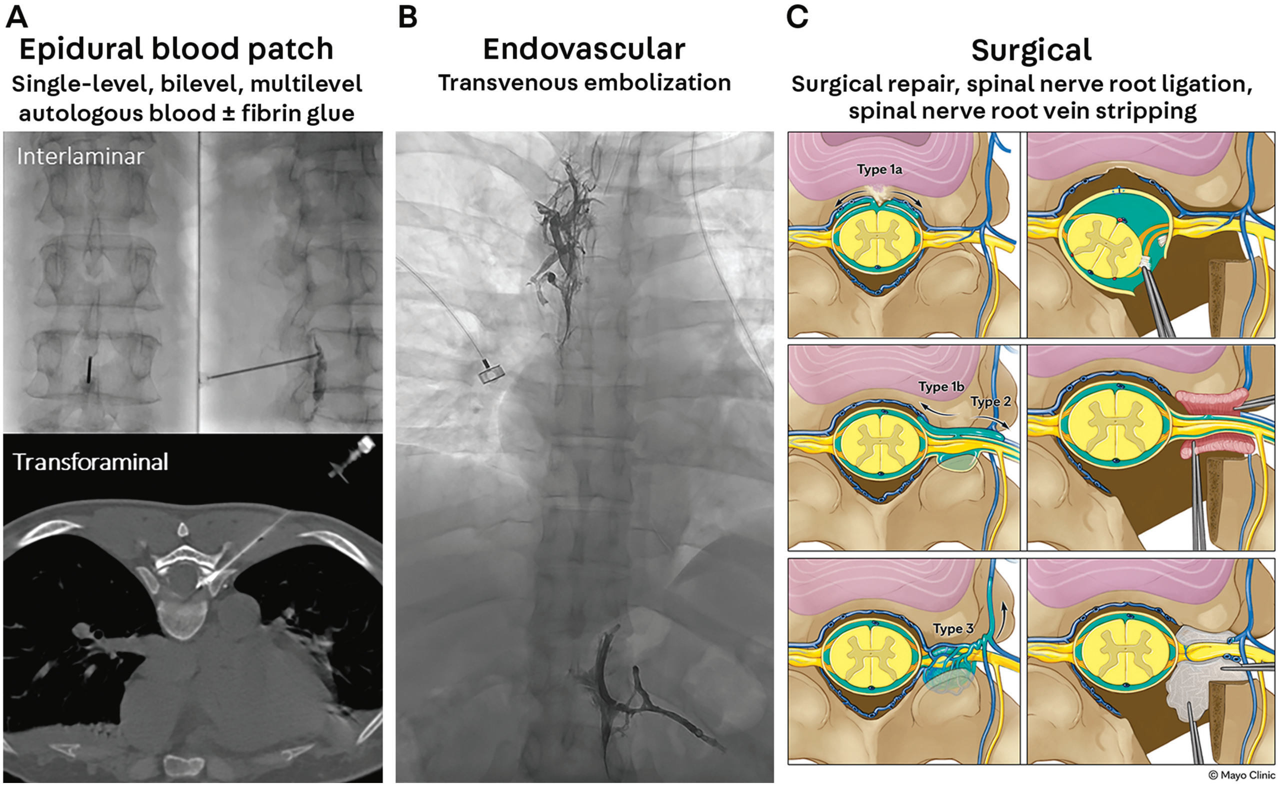
A
Epidural blood patch
Single-level, bilevel, multilevel autologous blood ± fibrin glue
Interlaminar
Transforaminal
B
Endovascular
Transvenous embolization
C
Surgical
Surgical repair, spinal nerve root ligation, spinal nerve root vein stripping
Type 1a
Type 1b
Type 2
Type 3
© Mayo Clinic

FIGURE 3-1

Treatment approaches for spontaneous intracranial hypotension vary depending on the type of CSF leak and radiographic features. *A*, Epidural blood patch with image guidance (CT or fluoroscopy) via interlaminar or transforaminal approach is dependent on the location of the CSF leak and available services at the performing institution. *B*, For CSF-venous fistulas, transvenous embolization has supplanted surgery as the preferred treatment modality at many institutions. *C*, In treatment-refractory spinal CSF leaks and other select cases, surgical repair requires confident localization of the CSF leak. Ventral dural tears (type 1a leaks) can be repaired via transdural or extradural approaches. For type 1b and type 2 leaks with nerve root sleeve tears or weeping diverticula, the defect of the nerve root sleeve is closed with a reduction of arachnoid bulges or diverticula when present. In CSF-venous fistulas (type 3 leaks) at nonappendicular levels (eg, thoracic level), a spinal nerve root ligation can be performed wherein a laminectomy with facetectomy is used for visualization.

Panel C used with permission from Mayo Foundation for Medical Education and Research. © 2025 Mayo Foundation for Medical Education and Research.

TREATMENT APPROACH

With advances in localization of spinal CSF leaks and the development of new therapeutic treatment options in recent years, the approach to the treatment of CSF hypovolemia continues to evolve. Treatment recommendations ultimately depend on available resources and the type of underlying leak, of which there are three main types: Type 1 leaks are dural tears of the main thecal sac (type 1a) or proximal nerve root sleeve (type 1b). Type 2 leaks are leaking meningeal nerve root sleeve diverticula. Type 3 leaks are fistulas, usually between the nerve root sleeve and one or more epidural veins. Evidence is growing that outcomes improve with earlier treatment. Using the best initial treatment based on clinical and radiographic features increases efficacy and minimizes adverse events from repeated procedures but may be limited by the availability of specialized treatments such as transvenous embolization and surgery (**FIGURE 3-2**).[9-11]

Before treatment, a patient with suspected spontaneous intracranial hypotension should undergo evaluation with MRI of the head and spine (cervical, thoracic, and lumbar)[10]; for more information about imaging in these patients, refer to the article “Radiographic Evaluation of Spontaneous Intracranial Hypotension” by Ajay A. Madhavan, MD, and J. Levi Chazen, MD,[12] in this issue of *Continuum*. While the patient is undergoing the initial imaging evaluation, supportive care (eg, hydration, abdominopelvic compression) should be implemented for up to 2 weeks, but if symptoms associated with spontaneous intracranial hypotension persist, then more definitive treatment should be pursued.[10] The imaging findings can then be used to direct treatment.

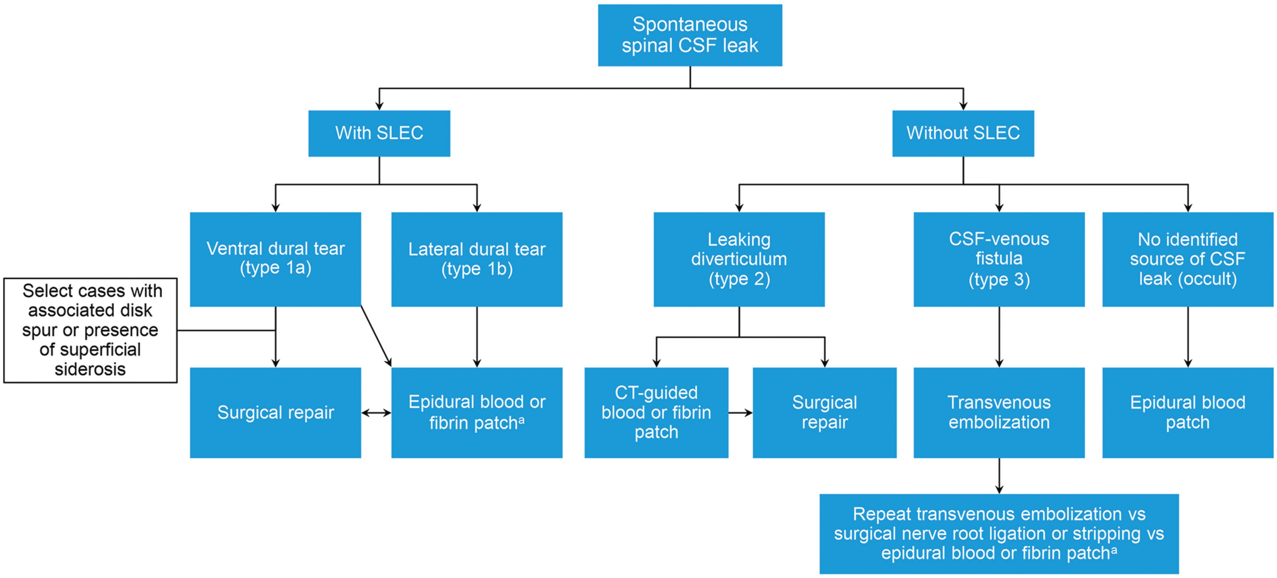
Spontaneous spinal CSF leak
With SLEC
Without SLEC
Ventral dural tear (type 1a)
Lateral dural tear (type 1b)
Leaking diverticulum (type 2)
CSF-venous fistula (type 3)
No identified source of CSF leak (occult)
Select cases with associated disk spur or presence of superficial siderosis
Surgical repair
Epidural blood or fibrin patch[a]
CT-guided blood or fibrin patch
Surgical repair
Transvenous embolization
Epidural blood patch
Repeat transvenous embolization vs surgical nerve root ligation or stripping vs epidural blood or fibrin patch[a]

FIGURE 3-2

The radiographic features, localization, type of CSF leak, and previous treatments are factors that guide treatment of spinal CSF leaks and CSF-venous fistulas.

SLEC = spinal longitudinal extradural fluid collection; vs = versus.

[a] Whenever the source of a CSF leak is identified, efforts should be made for a targeted therapy.

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Spinal longitudinal extradural fluid collections as observed on spinal MRI typically occur with either a ventral CSF leak (type 1a CSF leak) or CSF leak in the lateral recess (type 1b CSF leak with a proximal nerve root sleeve tear).[11] The presence of a spinal longitudinal extradural fluid collection is a predictor of a positive response to an epidural blood patch, so the patch is a typical initial treatment option when spinal longitudinal extradural fluid collections are present (FIGURE 3-2).[11] The type of image guidance and the decision to use fibrin in an epidural blood patch are discussed later in this article. Repeat epidural blood patch or surgery after initial epidural blood patch is common. In select cases with the presence of a spinal longitudinal extradural fluid collection, radiographic findings may direct the care team to forego an epidural blood patch and proceed directly with surgical repair. For example, the presence of superficial siderosis, which is associated with spontaneous intracranial hypotension and can cause irreversible cerebellar ataxia and sensorineural hearing loss, may direct the care team to earlier surgical repair.[13] Also, the presence of a disk spur or spiculated osteophyte (often called a *bony spicule*) may prompt consideration of earlier surgical repair.

Initial treatment with an empiric nontargeted blood patch has been common practice for spontaneous intracranial hypotension at most institutions. In patients with spontaneous intracranial hypotension and no spinal longitudinal extradural fluid collections, empiric treatment with a nontargeted epidural blood patch may delay more definitive treatment (eg, transvenous embolization or surgical correction) (FIGURE 3-2). Recent evidence also shows that patients with CSF-venous fistulas respond poorly to epidural blood patches. In a series by Duvall and colleagues,[14] for example, only 1 of 40 patients (2.5%) with CSF-venous fistulas who underwent epidural blood patch had a definitive response. In contrast, after surgical treatment in the same series, 20 of 42 patients (48%) were headache free, another 11 patients (26%) had 50% or greater improvement of headache, and only 8 (19%) had no improvement after surgical treatment. In another series by Kranz and colleagues,[15] only 3 of 22 patients (14%) had improvement after treatment with an epidural blood patch, whereas all patients showed improvement following surgery. Both of these studies predated the era of transvenous embolization to have as a comparator. At tertiary referral centers, CT myelography is often pursued before epidural patching to localize the source of CSF leak and direct treatment. In patients with a CSF-venous fistula, more recently and depending on the institution, initial treatment is often transvenous embolization, with surgical treatment or epidural blood patch with or without fibrin reserved for refractory cases. When a distal nerve root sleeve tear or weeping diverticulum (type 2 CSF leak) is identified, a transforaminal epidural fibrin patch should be performed, but surgical repair is also common in this scenario.[11] When no source of CSF leak is identified, an empiric multifocal epidural blood patch is typically performed. Careful review of the radiographic imaging of the spine is required before the epidural blood patch, and a targeted epidural blood patch at suspicious areas (eg, large diverticula, areas with hyperdense paraspinal vein) should be pursued when possible; note that some imaging findings may be nonspecific or falsely localizing.[16] If the treating facility does not have access to the appropriate myelography, transvenous embolization, or surgical treatment, then an empiric nontargeted epidural blood patch should be performed to prevent delays in care while patients with refractory cases are referred to a tertiary center that specializes in the treatment of spontaneous intracranial hypotension.[10]

KEY POINTS

- **Clinical outcomes after definitive treatment of spontaneous intracranial hypotension are better in patients with a shorter duration of symptoms.**

- **The presence of a spinal longitudinal extradural fluid collection observed on whole-spine MRI without contrast is a predictor of a positive response to an epidural blood patch, at least temporarily.**

- **The presence of superficial siderosis typically observed in the posterior fossa or an associated spiculated spinal osteophyte at the site of a CSF leak may direct a multidisciplinary care team to earlier surgical repair.**

SUPPORTIVE CARE

Supportive care should be implemented acutely in patients with suspected spontaneous intracranial hypotension to increase the chances of spontaneous resolution of the CSF leak and to improve outcomes following treatments. Encouraging hydration with 2.0 L to 2.5 L of fluids daily has minimal risk assuming no underlying renal or cardiovascular disease and has the potential for improving symptoms.[10] The evidence is limited for the use of abdominal binders in patients with spontaneous spinal CSF leaks, and guidelines for postdural puncture headache similarly do not endorse the routine use of abdominal binders for the treatment of postdural puncture headache.[17,18] In one comparative efficacy study of postdural puncture headache, similar clinical responses were observed with epidural blood patches and abdominal binders that were not observed in the control group.[19] Abdominal binders may increase pressure around the spinal canal, thereby reducing the pressure gradient from the intrathecal space to extrathecal space and reducing CSF flow.[17] Abdominal binders have been shown to provide some benefit in patients with overdrainage headaches after ventriculoperitoneal shunting with a suspected mechanism of modulating abnormally increased intracranial pulse pressures associated with overshunting.[20] The use of abdominal binders either acutely at initial symptom onset, following treatment, or in treatment-resistant spinal CSF leaks has limited evidence, but it may improve outcomes with a minimal potential for adverse events from use. Patients should be instructed to remove the abdominal binder when in the recumbent position and remain flat for several minutes to prevent a sudden onset of severe headache, which could occur if the abdominal binder was removed while upright.[21]

The use of bed rest in management is dependent on the duration of symptoms and intractability to treatment. In the acute presentation (first 2 weeks of symptoms), bed rest with fluid hydration and abdominal binders may result in spontaneous resolution of spinal CSF leaks.[21] Longer-term (months to years) bedrest can result in deconditioning, contribute to maladaptive behavior, and further confound disability. In long-term management, bed rest should be reserved for symptomatic treatment of severe headache exacerbations or following interventions.

MEDICATIONS

Headaches associated with spontaneous intracranial hypotension typically do not respond to abortive or preventive medications, but the use of caffeine on a limited basis up to 2 d/wk may be of benefit for severe exacerbations. Although caffeine is commonly used for acute management of postdural puncture headache, with studies showing some transient symptomatic improvement,[17,18] in animal models it counterintuitively appears to acutely reduce intracranial pressure. The analgesic effects of caffeine on CSF hypovolemic states may be independent of CSF volume and relate instead to vasoactive effects on the cerebral vasculature.[22] In animal models, chronic treatment with caffeine can increase intracranial pressure.[23] Further research is needed to understand the impact of caffeine use on CSF dynamics, and chronic use of caffeine in patients with spinal CSF leaks may be detrimental because long-term use may theoretically predispose a patient to rebound intracranial hypertension following definitive treatment of spinal CSF leaks. In patients with postdural puncture headache, studies have shown improvements in pain scores with the use of theophylline, corticosteroids, pregabalin, and cosyntropin, but the lack of sufficient quality evidence resulted in guidelines for postdural puncture headache recommending against the routine systemic administration of these drugs.[17,18,24] In addition, the evidence supports earlier treatment for patients with spontaneous intracranial hypotension, and symptomatic treatment with the previously mentioned medications should not postpone more definitive treatment.[9] For patients with an occult spinal CSF leak (with appropriate diagnostic imaging and no source found) and unsuccessful treatment with an epidural blood patch, medications such as theophylline and gabapentin may be of benefit, with gabapentin being a better option because of the preventive effects observed in primary headache disorders. Corticosteroids should be avoided because of the adverse events associated with chronic use. In the setting of postdural puncture headache, studies have not shown sumatriptan or adrenocorticotropic hormone to be effective.[24]

A proportion of patients with spontaneous intracranial hypotension may also have an underlying primary headache disorder, most commonly migraine. Treatment with abortives and preventives selected for headache phenotype may be beneficial for patients with occult spinal CSF leaks unresponsive to epidural blood patching, where treatment with tricyclic antidepressants (eg, nortriptyline, amitriptyline) may be particularly good options.[10] In the setting of spontaneous intracranial hypotension, topiramate should be avoided because of carbonic anhydrase activity and CSF pressure–lowering effects.[10] Indomethacin has been shown to decrease intracranial pressure acutely, which is unhelpful in the setting of CSF hypovolemia, and long-term effects are less clear, so it should be avoided in the context of spontaneous intracranial hypotension.[10,25] Case reports have shown postural orthostatic tachycardia syndrome to be associated with spontaneous intracranial hypotension, and in that setting, antihypertensive medications should be avoided.[10,26,27]

Studies of postdural puncture headache have investigated the use of epidural infusion of crystalloids, dexamethasone, morphine, dextran, gelatin, and hydroxyethyl starch, but the evidence did not show superiority to epidural blood patch, so guidelines for postdural puncture headache recommend against the routine epidural administration of any of these agents.[17,18,28] These recommendations can rationally be translated to the management of spontaneous intracranial hypotension. A case series of patients who had exhausted treatments for spontaneous intracranial hypotension showed promising symptomatic improvement with a chronic indwelling epidural catheter infusion system connected to an external pump infusing crystalloid, but the high rates of complications (eg, infection) limit the use of this approach to a select group with intractable symptoms at quaternary subspecialty care centers.[29] The use of peripheral nerve blocks such as occipital nerve blocks and sphenopalatine ganglion blocks may provide benefit in the treatment of postdural puncture headache under certain circumstances with short-term pain relief,[17,18] but in the setting of spontaneous intracranial hypotension, these measures should not delay evaluation or more definitive treatment.

EPIDURAL BLOOD PATCHING

An epidural blood patch starts with establishing sterile IV access to obtain sterile autologous blood. Sterility is maintained by covering the access site with an occlusive dressing. With postdural puncture headache, an epidural blood patch is often performed with landmark guidance with the patient in the lateral decubitus

KEY POINTS

- **CSF-venous fistulas respond poorly to epidural blood patches.**
- **Distal nerve root sleeve tears (type 2 CSF leaks) respond poorly to epidural blood patches.**

or upright position. Image guidance is not always used for postdural puncture headache due to its known site of CSF leak, and frequently these patients lack significant spondylotic disease (eg, postpartum patients). In patients with spontaneous intracranial hypotension, the source of CSF leak is often not apparent, and patients may have significant spondylotic disease that makes epidural access difficult. Therefore, image guidance (eg, fluoroscopy or CT) is routinely used for epidural blood patches at most institutions (**FIGURE 3-1**). Imaging of the spine should be performed before the epidural blood patch and include at least the lumbar region if that is the target of empiric patching, but often the entire spine is imaged early as part of the diagnostic evaluation of the underlying spinal CSF leak. With image guidance, epidural access is obtained with the patient in the prone position by using a larger-bore epidural needle to allow for the injection of blood. Next, blood is obtained from the sterile IV access site. A small volume of the initial autologous blood drawn should be discarded before injection into the epidural space to prevent coagulation during injection. The autologous blood is injected slowly and incrementally into the epidural space. During injection, the patient is asked about worsening headache or new back pain (often called *pressure paresthesia*). There is a direct correlation between the volume of blood injected and the development of low back pain during injection.[30] If pressure paresthesia occurs, the epidural injection of autologous blood is paused until the sensation abates. If pressure paresthesia does not improve after a brief pause, the saturation point has been reached, needles are removed from the epidural space, and an occlusive dressing is placed over the patch site.

Mechanism of Action

Evidence on the mechanism of action for epidural blood patches is limited. Studies have shown that the injection of blood does not cause a sealant effect and that blood placed in the epidural space does not produce any more inflammatory changes than routinely performed diagnostic lumbar puncture.[5,31] Studies have also shown that epidural pressure increases transiently during the injection of saline, donor blood anticoagulated with ethylenediaminetetraacetic acid, and other injectates into the epidural space, followed by a return to postdural puncture headache baseline within 10 minutes.[31,32] In contrast, injection of whole blood or fibrin results in a sustained increase in CSF pressure.[31] This suggests that coagulated blood products are effective because of their tamponade effect.[5,31] In one study, response to an epidural blood patch was independent of absolute pressure generated by blood patching, and another case report described resolution of headache after an epidural blood patch despite no measurable change in intracranial pressure.[33,34] These observations support a mechanism in which relative changes in pressure gradients sustained by a tamponade effect from the epidural blood patch result in decreased CSF flow from the intrathecal compartment to the epidural space, which then allows the dural rent to undergo normal reparative processes.[5]

Evidence for Use in Spinal CSF Leaks

The evidence for the use of an epidural blood patch in the treatment of spinal CSF leaks is largely derived from the literature for the treatment of postdural puncture headache. Several randomized controlled trials have demonstrated the therapeutic efficacy of epidural blood patches in the treatment of postdural puncture headache with success rates varying from 33% to 91%.[17,18] For spontaneous intracranial hypotension, the primary evidence is limited to observational studies with the first attempt at an epidural blood patch reported to be successful (defined as clinical improvement without need for further intervention) in 64% of patients, but the durability of a long-term response is not well established in the setting of spontaneous intracranial hypotension.[35,36] The response to an epidural blood patch has been observed to be influenced by several factors, including injectate, location, number of vertebral levels injected, and clinical features.[37]

Adverse Events With Epidural Blood Patching

With a long history of clinical use, the risk of major complications from epidural blood patches has been observed to be very low and is evidenced by the paucity of serious adverse events reported after epidural blood patches in prospective studies.[17,18,35] Nevertheless, case reports have described intrathecal hematoma, arachnoiditis, meningitis, subdural abscess, radiculopathy, spastic paraparesis, urinary and fecal incontinence, Terson syndrome, and other neurologic deficits following epidural blood patch.[17,18] At least one case has been reported of cauda equina syndrome after an epidural blood patch requiring surgical decompression.[38] The volume of blood injected is correlated with the potential for adverse neurologic outcomes.[39] The most common adverse event with epidural blood patches is back pain, which occurs in up to 54% of patients during the procedure and by some accounts more than 80% of patients on the following day.[17,18,35] In long-term follow-up after an epidural blood patch for treatment of postdural puncture headache, a minority of patients had prolonged back pain (19 of 118 [16%]) with a duration of backache that ranged from 3 to 100 days and an average duration of 27.7 days.[40]

A prospective observational study in postpartum patients showed that patients who received an epidural blood patch and those who were managed conservatively (ie, no epidural blood patch) for postdural puncture headache had higher rates of chronic backache and chronic headache than those who underwent uncomplicated epidural anesthesia.[41] In this study, a nonsignificant increase in the presence of chronic low back pain was observed between patients with postdural puncture headache who received an epidural blood patch and those managed conservatively.[41] No differences in chronic headache were observed between the patients with postdural puncture headache who were treated with epidural blood patch and those treated conservatively.[41]

In a larger prospective observational study, patients with postdural puncture headache who were treated with an epidural blood patch were found to have a higher rate of chronic low back pain at 3 months than those with postdural puncture headache who did not receive an epidural blood patch (17% versus 8.8%), but this should be taken in the context that the patients in the epidural blood patch group had higher baseline headache pain intensity.[42] Given that this difference was observed only in a very large sample size suggests a small effect size.[42] Patients should be counseled about these potential adverse events (both major and minor) before undergoing an epidural blood patch.[17,18]

Injection Factors That Affect Response to Epidural Blood Patching

In patients with postdural puncture headache, the location of CSF leak is known and in a location (ie, dorsal) that should respond favorably to interlaminar

KEY POINTS

- **Supportive care and medication treatment should not delay the evaluation and more definitive treatment of patients with suspected spontaneous intracranial hypotension.**
- **The mechanism of action for epidural blood patching is not related to a sealant effect by blood products.**
- **The suspected mechanism of action for epidural blood patching is related to a tamponade effect from the coagulated blood products that allows a dural rent to undergo normal reparative processes.**

epidural blood patch, which has allowed for standardization (eg, volume, approach) and more conservative techniques (single level).[17,18] With spontaneous intracranial hypotension, however, because the location of the CSF leak varies and the type of CSF leak has an impact on outcomes, various considerations are needed to improve long-term outcomes, minimize the need for repeat epidural blood patch, and shorten the duration from symptom onset to resolution. Injection factors that affect the response to an epidural patch include the following:

- **Injectate volume**
- **Known versus empiric target**
- **Number of levels (single, bilevel, multilevel)**
- **Approach (interlaminar versus transforaminal)**
- **Type of injectate (autologous blood versus fibrin)**

A 2023 guideline for the management of spontaneous intracranial hypotension at nonspecialist centers recommends an empiric nontargeted epidural blood patch with a volume of 20 mL to 40 mL of autologous blood if symptoms persist after 2 weeks of conservative treatment.[10] After a failed nontargeted blood patch or at a specialty center, a higher injectate volume as tolerated by the patient may increase the efficacy of an epidural blood patch, but the higher volume increases the risk of adverse events.[37,39] If there is a suspected location of the spinal CSF leak, a blood patch targeted to the site of the suspected CSF leak may improve outcomes.[37] Comparisons of outcomes in targeted and nontargeted epidural blood patches showed similar proportions of successful results between the two approaches,[35] but that study did not take into account that targeted epidural blood patches are often reserved for patients for whom nontargeted blood patches have already failed.

The number of levels can be one, two, or multiple (three or more), depending on the institution. The number of vertebral levels targeted appears to have an impact on clinical outcomes and likely relates to the ability to inject more volume when more levels are accessed.[37] The volume of the epidural space is greatest in the lumbosacral spine segment, so this region can typically accommodate larger injections, and common practice is to include one site in the lumbar spine.[37] Often in occult (ie, no source of CSF leak identified) spinal CSF leaks, a high-volume bilevel blood patch is pursued with one site in the lumbar spine (capacity for volume) and the other site in the low thoracic spine (common CSF leak location).[35,37] Generally, single-level and bilevel epidural blood patches are performed with fluoroscopic guidance whereas multilevel epidural blood patches are performed with CT guidance, but image guidance may depend on availability at the performing institution. Epidural blood patches are typically performed either through a dorsal interlaminar (most common) or transforaminal approach (**FIGURE 3-1**), but a caudal approach through the sacral hiatus has also been described.[37,43]

The needle approach has an impact on clinical outcomes following epidural blood patch, and the decision on needle approach (transforaminal versus interlaminar) depends on the suspected location of the spinal CSF leak and anatomic considerations with each patient (eg, prior laminectomy, presence of neural foraminal stenosis). CT guidance is often used when a transforaminal needle approach is desired, especially in the thoracic and cervical spinal segments (FIGURE 3-1). Autologous blood or fibrin or both can be used as the injectate; the unlabeled use of fibrin is typically reserved for cases refractory to prior epidural blood patch with autologous blood and in the presence of a highly suspicious or confirmed site of leakage. Fibrin injection volumes are typically quite low and will not spread across multiple segments as blood can. Although some evidence shows that fibrin patches are more effective than autologous blood for epidural patches,[41] fibrin carries the potential risk of a hypersensitivity reaction (even anaphylaxis) and aseptic meningitis and is derived from human plasma, so it has the theoretical risk of transmitting infectious agents (eg, viral or prion disease). Given these risks, fibrin should be reserved for patients with a previous failure of autologous blood, patients with a contraindication to the use of autologous blood, or patients with a distal nerve root sleeve tear.[11,17,18] Smaller injectate volumes are typically used with fibrin when compared with autologous blood with some recommendations for fibrin only to be administered via transforaminal approach.[37,44]

Patient Factors Affecting Epidural Blood Patch Response

In addition to technical factors, patient factors affect the outcomes of an epidural blood patch. As discussed in the Treatment Approach section in this article, patients with a spinal longitudinal extradural fluid collection present on spine MRI often respond favorably to epidural blood patching.[11] These CSF leaks with spinal longitudinal extradural fluid collections (type 1a and type 1b leaks) collect within the central spinal canal, which allows blood products from an epidural blood patch to tamponade a CSF leak when contained by the surrounding bony elements. Meningeal nerve root sleeve diverticula that leak distally (type 2 leaks) and CSF-venous fistulas (type 3 leaks) mostly lie outside the epidural compartment (without surrounding bony vertebral elements) and, so, are less likely to respond to epidural blood patch.[11]

An underlying history of migraine may influence the response to an epidural blood patch. In the setting of postdural puncture headache, patients with a history of migraine were more likely to require a second epidural blood patch when compared with those without a prior history of migraine.[45] An underlying history of primary headache disorder should be addressed and treated, especially in the context of treatment-refractory spontaneous intracranial hypotension.[8] Patients with clinical features commonly associated with idiopathic intracranial hypertension (eg, female sex, obesity, tetracycline antibiotic or retinoic acid derivative use, polycystic ovary syndrome) may have underlying idiopathic intracranial hypertension, which may decrease effectiveness of an epidural blood patch or predispose to recurrent CSF leaks.[46,47] Some patients may develop rebound intracranial hypertension following an epidural blood patch. Rebound intracranial hypertension and a trial of acetazolamide should be considered when patients have persistent headache after an epidural blood patch, especially when there is a change in character of headache, such as if headache worsens when the patient is recumbent overnight rather than upright during the day or if the distribution flips from occipital to frontal or periorbital.[48]

Periprocedural Measures to Optimize Outcomes

In addition to supportive care as described earlier, measures can be taken to optimize clinical outcomes following an epidural blood patch for spinal CSF

KEY POINTS

- **The frequency of serious adverse events with epidural blood patching is very low but can include intrathecal injection causing hematoma and arachnoiditis, serious infection, or a compressive spinal syndrome requiring surgical intervention.**
- **Patients with postdural puncture headache who are treated with epidural blood patching have higher rates of chronic low back pain than those who were not treated with an epidural blood patch.**
- **A higher volume of injected autologous blood during epidural blood patch increases the efficacy but comes with a potentially increased risk of adverse neurologic events.**
- **When the source of a spinal CSF leak is identified, a targeted blood patch at the level of the CSF leak may improve clinical outcomes.**
- **The use of fibrin as an injectate in epidural blood patching carries added risks over autologous blood alone and should be reserved for patients with prior treatment failure with autologous blood or a contraindication to use of autologous blood or in locations of CSF leaks unlikely to respond to epidural blood patch.**

leaks. Immediately after an epidural blood patch, patients should be monitored in a recovery area followed by rest for a minimum of 2 to 24 hours.[10] In the recovery area, the patient should be placed in a supine and ideally Trendelenburg position (head declined to 30 degrees) for a minimum of 1 hour as tolerated by the patient. In postdural puncture headache, outcomes improved the longer a patient was kept in the supine position after an epidural blood patch (30 minutes versus 60 minutes versus 120 minutes).[49] There is some evidence that placement in the Trendelenburg position for up to 24 hours before and after an epidural blood patch may improve outcomes, with some patients reporting a spontaneous resolution of headache with this technique.[50,51]

After a targeted epidural blood patch, the authors start with the patient in the supine position. If they have worsening headache after the epidural blood patch, they are placed in a reverse Trendelenburg position if there is a high suspicion for rebound intracranial hypertension.[10] Patients should not drive themselves home after an epidural blood patch; rather, they should lie flat as much as possible for up to 3 days after the procedure. Thereafter, they should minimize activities that increase intracranial pressure (eg, coughing, straining, sneezing, bending over, heavy lifting, strenuous exercise) for 4 to 6 weeks after treatment; the recommended duration varies widely across institutions and providers.[10] Patients should be advised when to seek care after treatment based on the risks discussed during the informed consent (eg, new lower extremity weakness, incontinence, intractable pain, vision loss).[10] The possibility of rebound intracranial hypertension along with suggestive symptoms (eg, visual changes, supine or overnight headache) should be discussed before treatment.[10] There is some evidence that periprocedural acetazolamide may improve clinical outcomes after epidural blood patch,[50] but prophylactic acetazolamide is not routinely used at most institutions, and the authors reserve this medication for patients who develop suggestive symptoms within days of leak treatment.[10] In some instances, empiric treatment with carbonic anhydrase inhibitors for a short course (eg, 2 to 6 weeks) may be considered after treatment if there is a high suspicion the patient will develop rebound intracranial hypertension (eg, underlying idiopathic intracranial hypertension, long duration of symptoms or suspected CSF leak, radiographic evidence of diffuse calvarial hyperostosis).[47,52,53]

TRANSVENOUS CSF-VENOUS FISTULA EMBOLIZATION

Transvenous embolization of CSF-venous fistulas is emerging as a highly effective, minimally invasive treatment for direct obliteration of the draining veins involved in the CSF-venous fistula. The advantage of embolization is that occlusion of the fistula is achieved without a surgical wound, laminectomy, or sacrifice of the adjacent nerve root. Embolization is also performed with a permanent embolic agent (eg, ethylene-vinyl alcohol copolymer) rather than fibrin glue or autologous blood, which degrade within days or weeks.

The main objective of embolization is to occlude the specific site of CSF egress into the venous system, which is typically located at the foraminal venous plexus, also known as the *intervertebral venous plexus*, immediately adjacent to the exiting nerve root sleeve. To ensure complete CSF-venous fistula occlusion, given the vastly redundant nature of the venous system and numerous tributaries, it is recommended to occlude all the adjacent tributaries to the foraminal venous plexus, which commonly includes channels to the adjacent longitudinal epidural venous plexus, segmental paraspinal vein, intercostal vein, muscular paraspinal branches, and basivertebral vein (FIGURE 3-1). The specific veins to be occluded dictate the appearance of the embolic cast and may vary by patient. Careful study of the draining vein, on either preprocedural CT myelogram or digital subtraction myelogram, is needed to ensure it and origins of the adjacent venous tributaries are fully included in the embolic cast because it is not practical to perform lateral decubitus myelograms during the procedure to confirm complete fistula occlusion. To prevent embolic agent reflux into nontarget veins, coils or balloon microcatheters may be used to help guide and confine the embolic material into the foraminal venous plexus.[54,55]

Embolization is performed with the patient under general anesthesia or moderate sedation depending on patient and operator preference. Venous access is typically achieved at the femoral vein, but upper extremity access may also be used. The subsequent venous route from the puncture site to the foraminal venous plexus depends on the specific side and level of the fistula. A 2022 review article describes the typical venous anatomy and navigation routes for CSF-venous fistulas at specific levels.[56] For example, navigation to the most common CSF-venous fistula locations in the right lower thoracic spine, from right T5 to T12, is achieved by first accessing the azygos vein from the superior vena cava using a guide catheter. Subsequently, a microcatheter is navigated to the foraminal venous plexus from the guide catheter. Other common venous routes include navigation through the vertebral veins to access cervical fistulas, superior intercostal veins for upper thoracic fistulas, and hemi-azygos or accessory azygos veins for left-sided thoracic fistulas. Preprocedural venous navigation planning is critical to a smooth and efficient procedure. Venous catheter navigation is safe, straightforward, and well tolerated by patients, but navigation may be challenging for operators because of venous valves or variant or tortuous anatomy. For difficult anatomy, alternative venous routes for microcatheter navigation may be needed; for example, adjacent spinal levels can often be accessed through microcatheter navigation along the lateral epidural venous plexus. After the procedure, patients are recommended to lie flat for at least 1 to 2 hours and are either admitted for overnight observation or discharged after recovery from sedation or anesthesia.

Evidence

Transvenous embolization was first described as a novel treatment for CSF-venous fistulas by Brinjikji and colleagues[57] in 2020. In the initial report of five patients with spontaneous intracranial hypotension due to CSF-venous fistula treated with embolization, four patients had complete resolution of symptoms and one patient had 50% improvement following treatment. Brain MRI findings of spontaneous intracranial hypotension improved in all patients, with complete resolution in three and residual features in two. A subsequent series of 100 consecutively treated patients reported from the same center confirmed the early results, with 95 of 100 patients (95%) reporting resolution or improvement of symptoms after embolization; 58 had complete resolution, 37 had partial improvement, and 5 had no improvement.[58] Of 96 patients with baseline headache, 72 reported resolution of headache, 19 reported partial improvement, and 5 had no improvement. The mean clinical follow-up duration was 15.0 ± 6.8 months. Regarding imaging outcomes, 81 patients had improvement in their Bern spontaneous intracranial hypotension scores on

KEY POINTS

- **Patients with refractory headache following a thorough evaluation and treatment of spontaneous intracranial hypotension should be evaluated for an underlying primary headache disorder and treated accordingly.**
- **Transvenous embolization is an effective treatment of CSF-venous fistulas with low rates of adverse events but requires confident localization of the CSF-venous fistula.**

brain MRI, whereas 3 had no change. Fourteen patients had a baseline Bern spontaneous intracranial hypotension score of 0 and no radiographic worsening after treatment. Although derived from a single center, this series of patients represents one of the largest treatment studies for CSF-venous fistula of any modality reported to date.

These single-center results have been reproduced at multiple centers worldwide. In the current literature, at least five separate single-center case series,[54,59-62] as well as a 2024 systematic review,[63] demonstrate positive results similar to those presented from the originating center. The largest independent validation cohort of the technique was reported by Parizadeh and colleagues[54] in 18 patients with CSF-venous fistula. In this study, 89% of patients reported much or very much improved symptoms 3 months after embolization based on the Patient Global Impression of Change scale. Headache severity based on the six-item Headache Impact Test improved from a median of 68 before treatment (considered severe impact) to 36 after treatment (little to no headache). Brain MRI spontaneous intracranial hypotension findings improved from a median Bern spontaneous intracranial hypotension score of 8 (6 to 8) to 3 (1.5 to 3.5) with 88% of patients showing improvement from the initial abnormal brain MRI. A recent systematic review of 77 patients showed that 84% had complete resolution or significant improvement in symptoms following CSF-venous fistula embolization.[63] Overall, these results are similar to if not better than results from surgical treatment studies and appear to be more consistent than those reported for targeted fibrin patching. Further long-term and multicenter data are required.

Adverse Events

Transvenous embolization is considered safe, and to date, no severe neurologic complications have been reported.[58,63] The most common symptoms after treatment include back pain and transient rebound intracranial hypertension that may occur in as many as 30% to 50% of patients and may require the use of acetazolamide. Some degree of rebound intracranial hypertension including head pressure, typically frontal and worse with recumbency and different from the patients' original headache, may be seen in up to 70%.[54,60,63] Transient local pain at the level of embolization may be seen in 35% to 80% of patients and generally resolves in 1 to 4 weeks.[54,63] Brinjikji and colleagues[58] reported intraoperative complications of ethylene-vinyl alcohol copolymer emboli in pulmonary arteries in one patient (2.5%) and paraspinal vein perforation without clinical sequelae in two patients (5%). Parizadeh and colleagues[54] also reported 4 of 18 patients (22%) with intraprocedural epidural or paravertebral contrast or embolic agent extravasation, but these were all asymptomatic and had no clinical sequelae.

The procedure fails to improve symptoms in 5% to 10% of patients.[54,63] This failure may be the result of incorrect targeting if the diagnostic myelogram is misinterpreted or fails to show multiple concurrent fistulas, incomplete occlusion of the CSF-venous fistula, or early recurrence of an otherwise properly treated CSF-venous fistula. Proceduralists must be thorough and precise with the embolization based on the techniques described earlier. Incomplete embolization may be subsequently treated with either additional embolization, targeted fibrin patching, or open surgery. A 2022 series demonstrated positive results for surgical treatment after unsuccessful embolization.[64] Residual or recurrent symptoms may also be caused by de novo CSF-venous fistulas at new levels (**CASE 3-1**).[58,59,65]

SURGICAL CORRECTION

As for other treatment modalities, the technique for surgical repair depends on the location and type of spinal CSF leak. Posterolateral, lateral, anterior, and midline approaches have all been described and typically require exposure with hemilaminectomies, full laminectomies, laminotomies, or occasionally endoscopic visualization.[66-68] Intraoperative neuromonitoring with motor evoked potentials and somatosensory evoked potentials should be considered, particularly if a midline approach with a spinal cord release maneuver is used.[66] Techniques for closure also vary and may involve use of an absorbable gelatin sponge, packing, muscle pledgets, buttressing with muscle, suturing of the dural defect, closure with microclip sutures, dural patch with fibrin, dural grafts or sealants, and reduction of arachnoid bulges or diverticula (FIGURE 3-1).[66-68] Ventral (type 1a) leaks are often associated with a disk osteophyte or a bone spur (also called a *bony spicule*) that requires removal with diskectomy.[69] In some cases, the disk osteophyte may resorb spontaneously, but the CSF leak can persist and still require repair.[70,71] It is reasonable to forego an epidural blood patch and proceed directly to surgical repair when a CSF leak is associated with a prominent, protuberant, or heavily calcified disk osteophyte complex or when superficial siderosis is present.[9,13]

For patients with CSF-venous fistulas, surgical repair with spinal nerve root ligation or nerve root stripping was the treatment of choice before the recent advent of transvenous embolization.[72,73] Observational studies have shown improvements in headache and other neurologic symptoms, as well as radiographic improvements, following surgical repair of CSF-venous fistulas.[72] With spinal nerve root ligation, a laminectomy with facetectomy is performed for visualization. The root is typically ligated with sutures (often with the use of a temporary clip), amputated just distal to the suture and proximal to the dorsal root ganglion, and then the empty foramen is packed with muscle, absorbable gelatin sponge, and fibrin (FIGURE 3-1).[72] Nerve root ligation surgery has two major limitations: (1) the level of the CSF-venous fistula must not be at an appendicular level (eg, nerve root that supplies the upper or lower limb), and (2) the artery of Adamkiewicz or a large radiculomedullary artery must not be present at the level of the intended treatment because the arterial vasculature is also sacrificed with the spinal nerve root. Major complications are minimized with identification of the level using preoperative gold seed placement into a pedicle for intraoperative spinal level confirmation and angiography to map the arteries. In the cases of CSF-venous fistulas at appendicular levels or with an associated key artery, nerve root stripping can be performed in which veins in the area of the root are cauterized and stripped from the root and the foramen is packed with muscle, an absorbable gelatin sponge, and fibrin.[72]

Lumbar dural reduction surgery has been described for intractable cases of spontaneous intracranial hypotension, but it does not resolve the underlying leak and is of questionable benefit.[74]

Evidence

The evidence for treatment of spinal CSF leaks via surgical approaches is limited to more retrospective than prospective observational studies.[36,67] The surgical outcomes have been variably described, generally with small sample sizes and heterogeneous mixtures of surgical approaches.[36] In that context,

KEY POINTS

- A disk spur associated with a ventral (type 1) CSF leak may resorb on its own, while the CSF leak can persist and still require surgical repair.
- Surgical repair of CSF-venous fistulas with spinal nerve root ligation requires sacrificing the nerve root at the level of the CSF-venous fistula and, to prevent disabling extremity weakness, should be avoided at appendicular levels.
- In surgical repair of CSF-venous fistulas with spinal nerve root ligation, the arterial supply at the treated level is sacrificed, and the artery of Adamkiewicz or large radiculomedullary arteries should be identified preoperatively with angiography so they can be avoided during treatment.
- Surgical repair of CSF leaks yields durable treatment responses.
- Postsurgical CSF leaks are less likely to respond to blood patching and often require surgical repair.
- After treatment, if symptoms persist and clinical suspicion for a persistent CSF leak is low, a nuclear medicine cisternogram can help provide objective evidence of the persistence or resolution of the CSF leak.

surgical repair of dural defects has shown durable treatment responses with resolution of symptoms in the majority of patients (62%) during a mean duration of follow-up of 20.5 months.[68] Long-term resolution of symptoms has been reported in 70% of patients with CSF-venous fistulas treated by surgical ligation.[73] Adverse events vary based on the type of surgical approach and include paresthesia, numbness, back pain, cranial nerve deficits, appendicular weakness or paraparesis, urinary retention, myelopathy, and epidural hematoma requiring evacuation.[66,68,73]

CASE 3-1

A 57-year-old woman with a history of episodic migraine with aura presented to a neurologist after 4 months of a new headache distinctly different from her previous migraine headaches. She developed an orthostatic headache that started each day within 30 minutes of rising from bed, worsened as the day progressed, and improved when she was in a recumbent position. She noted that coughing would provoke a headache, and she had more severe headache exacerbations up to 6 times a day that lasted about 15 minutes each. The headache was bioccipital and throbbing. Propranolol 40 mg 2 times per day yielded minimal improvement in the headaches over 2 months, and her prior migraine abortive medications of ibuprofen and rizatriptan were not effective for the new headaches. Her brain MRI was normal without evidence of brain sagging or pachymeningeal enhancement, and spinal MRI did not show extradural fluid collections (FIGURE 3-3). Initial prone CT myelogram did not identify the source of a CSF leak, and an empiric epidural blood patch at the L2-L3 level with 25 mL of autologous blood provided no headache relief. A lateral decubitus digital subtraction myelogram later showed a clear CSF-venous fistula at the right T5 level and a possible CSF-venous fistula at the left T1 level (FIGURE 3-3). With the more definitive findings at the right T5 level (a nonappendicular nerve root), the clinical decision was made to proceed with a right T5 spinal nerve root ligation.

Following a right T5 spinal nerve root ligation, the patient was headache free for 4 years other than her typical migraine headaches occurring about once a year. Four years after initial treatment, she had a recurrence of a similar orthostatic and cough headache. Repeat MRI of her head did not show evidence of spontaneous intracranial hypotension, similar to the previous imaging, and spine MRI did not show extradural fluid collections. A lateral decubitus digital subtraction myelogram showed a new right T12 CSF-venous fistula. She then underwent transvenous embolization at the right T12 level and remained headache free throughout 3 months of follow-up.

COMMENT

This case highlights the importance of myelography in diagnosing and localizing CSF-venous fistulas and directing treatment when there is a high index of clinical suspicion for spontaneous intracranial hypotension, even with normal MRI of the brain and spine.

Lumbosacral CSF Leak Treatment Considerations

Suspected CSF leaks in the lumbosacral spine can be particularly challenging. Diagnostic localization can be difficult because typical patient positioning for myelography does not allow the flow of contrast from the lumbar access site toward the sacral levels. Visualizing the lumbosacral source of a CSF leak often requires techniques using the reverse Trendelenburg position. Patients with suspected lumbosacral CSF leaks often have a history of previous lumbar spine surgery or underlying connective tissue disease (eg, Marfan syndrome) with

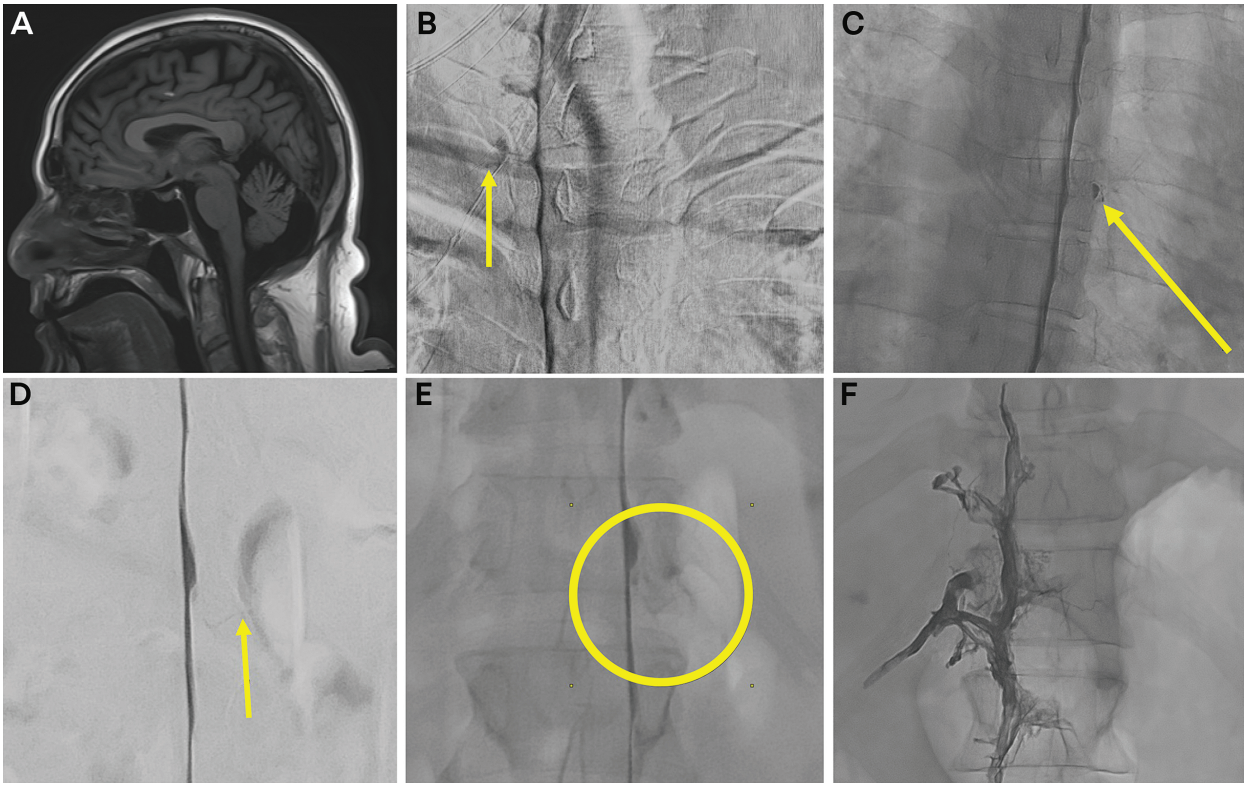

FIGURE 3-3

Imaging findings from the patient in CASE 3-1. *A*, Sagittal T1-weighted sequence brain MRI shows no brain sagging or pachymeningeal enhancement. *B*, A lateral decubitus CT myelogram shows a possible left T1 CSF-venous fistula (*arrow*). *C*, A more definitive finding for a CSF-venous fistula was identified at the right T5 level (*arrow*), which was eventually treated with a right T5 spinal nerve root ligation. *D*, After recurrence of orthostatic and cough headache, a new right T12 CSF-venous fistula was observed (*arrow*). *E*, Magnified view of the image showing the right T12 CSF-venous fistula (*circle*). *F*, Posttreatment x-ray after transvenous embolization of the right T12 CSF-venous fistula, which resulted in resolution of orthostatic and cough headache.

large sacral cysts. Postsurgical CSF leaks are less likely to respond to blood patching and often require surgical repair.[75] With suspected sacral CSF leaks, conservative treatments alone may be effective.[76] Targeted blood patches can be effective in the treatment of sacral CSF leaks.[77,78] More recently, a small number of sacral CSF-venous fistulas have been identified and treated with transvenous embolization.[79] Surgical repair of a sacral dural defect may be indicated, especially in the context of superficial siderosis.[80]

RECURRENT CSF LEAKS AND FISTULAS

Recurrent CSF leaks and CSF-venous fistulas can occur regardless of the treatment modality (epidural blood patch, transvenous embolization, or surgical repair) and can be at the site of the initial CSF leak or in new locations.[35,58,65,72,81,82] Regular follow-up is important to assess treatment response. MRI of the head is typically performed after treatment to establish a new imaging baseline after resolution of symptoms because improvements on imaging correlate with clinical improvements.[58,72,83] If patients have recurrent headache or other symptoms suggestive of spinal CSF leak, the most appropriate next step is usually brain MRI without and with gadolinium contrast for comparison to previous imaging. Depending on the type of the previous CSF leak and treatment, myelography is often repeated with the goal of confirming CSF leakage at a new or the original site and thus directing targeted therapy. If suspicion is high for recurrent CSF hypovolemia but no CSF leak or CSF-venous fistula is identified on myelography, then an epidural blood patch is often pursued. In some instances of symptom recurrence after transvenous embolization of a CSF-venous fistula with negative repeat myelography, repeat transvenous embolization at the previously treated level with expansion immediately above and below the previous site of embolization (ie, a “patch sandwich”) may be pursued.[58] Otherwise, surgical ligation as discussed earlier at the site of previous transvenous embolization has also been successful in refractory cases.[64] If any doubt exists regarding the recurrence of symptoms being related to CSF hypovolemia, radioisotope cisternography can help assess for indirect signs of persistent spinal CSF leak, such as early tracer activity in the bladder and reduced tracer activity over the cerebral convexities at 24 hours. If MRI, cisternogram, and myelogram do not suggest active spinal CSF leak, clinicians should consider optimizing treatment of any underlying primary headache disorder or evaluating and treating mimics of spontaneous intracranial hypotension such as cervicogenic headache and orthostatic intolerance.

CONCLUSION

With the rapid advancements in diagnosis and treatment of spinal CSF leaks and CSF-venous fistulas in recent years, our ability to help patients with spontaneous intracranial hypotension has expanded dramatically and improved clinical outcomes. Early diagnosis and definitive treatment appear to improve symptom response, and the radiographic findings can guide treatment (FIGURE 3-2). When possible, treatment with the highest likelihood of efficacy should be pursued as available at the treating institution without delays in care and referrals to subspecialty centers as necessary.

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Clinical Features and Diagnosis of Idiopathic Intracranial Hypertension

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: Idiopathic intracranial hypertension (IIH) is a condition of unexplained increased intracranial pressure. This article provides an overview of the process of diagnosing IIH and summarizes health disparities and potential barriers to care facing patients with IIH.

LATEST DEVELOPMENTS: Population studies have shown that IIH incidence increases with the rising rates of obesity, with subsequent financial burden and potential implications for the health care system. There may be ethnic or racial differences in IIH prevalence, and the degree to which social determinants of health affect these differences requires further exploration.

ESSENTIAL POINTS: IIH, a syndrome secondary to increased intracranial pressure without an underlying structural cause, can lead to disability, including blindness. Overdiagnosis of IIH has led to overutilization of health care resources. This article presents the criteria for diagnosing IIH, possible biases that may affect clinical reasoning, and approach to early referral to the appropriate clinical experts.

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is a condition characterized by symptoms and signs of unexplained elevated intracranial pressure (ICP) in an alert and awake patient. IIH falls under the broader category of pseudotumor cerebri syndrome, wherein there is no space-occupying lesion causing the intracranial hypertension.[1] IIH is a diagnosis of exclusion, and it is important to exclude possible secondary causes of intracranial hypertension aside from brain tumors, such as venous sinus thrombosis and infection that necessitate directed management and therapy. IIH was previously known as *benign intracranial hypertension*, but this terminology is misleading because the condition has potentially devastating effects on vision, headache burden, increased cardiovascular disease risk, sleep disturbance, and depression.[2-4] It is crucial to recognize IIH to prevent disability related to blindness and to improve patients' quality of life.

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EPIDEMIOLOGY

Understanding the incidence and prevalence of IIH, its social determinants, and the burden of caring for patients with IIH helps identify gaps in care that may lead to better IIH health care delivery.

Incidence and Prevalence of Idiopathic Intracranial Hypertension

IIH is commonly seen in women with a body mass index [BMI] greater than 30 kg/m^2 and of reproductive age (15 to 44 years old), with a median annual incidence of 1.97 per 100,000 in women versus 0.36 per 100,000 in men from 1997 to 2016 in the United States.[5] There was a 1.35-fold increase in prevalence in the United States from 11.3 female individuals per 100,000 in 2015 to 15.4 female individuals per 100,000 in 2022.[6] In the United Kingdom, there was a 108% increase in IIH incidence from 2.26 to 4.69 per 100,000 from 2002 to 2016.[7] These increases parallel the increasing rates of obesity worldwide.[8]

The annual incidence of IIH was 0.6 per 100,000 Canadian children and 0.71 per 100,000 British children.[9,10] There was no sex predilection for IIH among Canadian children, but this was only true for those younger than 7 years old in the British cohort. The incidence in girls was double that in boys for British children 7 years old and older. Adolescent patients with IIH were more likely to be obese than were the younger patients with IIH.[9,11]

IIH is associated with metabolic conditions such as obesity, weight gain, polycystic ovarian syndrome, and obstructive sleep apnea (CASE 4-1).[12-14] For more information about the pathophysiology of IIH, refer to the article

CASE 4-1

A 22-year-old transgender man, with a body mass index (BMI) of 36.1 kg/m^2, presented with headaches, transient visual obscurations, pulsatile tinnitus, cecocentral scotomas, and Frisén grade 5 papilledema. Brain MRI and MR venography were normal. CSF opening pressure was elevated at 29 cm H_2O, and CSF studies were normal. His idiopathic intracranial hypertension (IIH) resolved with acetazolamide 4000 mg daily and a left optic nerve sheath fenestration, but he was left with residual bilateral optic neuropathy. His IIH symptoms (headaches, transient visual obscurations, and pulsatile tinnitus) recurred 2 years later. He had bilateral Frisén grade 3 papilledema, recurrent retinal nerve fiber layer elevation on optical coherence tomography, and a worse cecocentral scotoma in his left eye that extended inferotemporally. Repeat brain MRI and MR venography were normal. Opening pressure was elevated at 29 cm H_2O with normal CSF studies. Acetazolamide 4000 mg daily was ineffective, and the IIH resolved only after a repeat optic nerve sheath fenestration. He was able to continue gender-affirming intramuscular testosterone therapy safely and was undergoing serial neuro-ophthalmic surveillance.

COMMENT

This case illustrates the management of IIH in a transgender man. Typical treatments for IIH should be pursued, and treatment does not require stopping gender-affirming hormonal therapy.

"Treatment and Monitoring of Idiopathic Intracranial Hypertension" by John J. Chen, MD, PhD, and Susan P. Mollan, MBChB, PhD, FRCOphth,[15] in this issue of *Continuum*.

Social Determinants of Idiopathic Intracranial Hypertension

The highest prevalence of IIH was seen in Black, White, and Hispanic people in the United States, which may be related to the higher obesity prevalence, limited access to healthy food, and increased barriers to health insurance access in these populations.[5,6,16,17] Several studies have found that patients with IIH are more likely to have a lower socioeconomic status or be unemployed.[5,7,17,18] In the United States, women with IIH were likely to delay care because of rural residence, limited access to transportation, and inability to afford the copay or the cost of seeing a specialist.[17] The risk of severe visual loss is higher in Black patients with IIH than in White, Hispanic, and Asian patients with IIH.[19]

Burden of Caring for Patients With Idiopathic Intracranial Hypertension

In 2016 to 2017, a cohort of patients with IIH selected from 32 million patient-years of population-level data in Wales, United Kingdom, had a mean rate of 0.54 unscheduled hospital visits per patient per year, significantly higher than the control cohort that had a mean rate of 0.10 hospitalizations per patient per year.[20] In the United Kingdom, from 2002 to 2016, the estimated annual hospital health care cost was £7116 (US $8684) per patient with IIH, and the total cost of IIH hospital care for these patients rose from £9.2 million (US $11.0 million) in 2002 to £49.9 million (US $60.9 million) in 2014. If the IIH incidence continues to follow this increasing trend, by 2030, the projected cost in the United Kingdom alone is £462.7 million (US $564.6 million).[7] In the United States, the total costs of IIH care was greater than $444 million in 2007, wherein almost half of the cost resulted from lost wages and other nonmedical expenses, and the rest was due to direct medical and surgical hospital expenses.[21]

DIAGNOSING IDIOPATHIC INTRACRANIAL HYPERTENSION

Diagnosis of definite, probable, or possible IIH is based on the modified Dandy criteria (TABLE 4-1[22]), wherein secondary causes of increased ICP (TABLE 4-2[23]) are excluded with thorough neurologic and ophthalmologic evaluation, neuroimaging, and CSF analysis.[22,24] ICP is considered elevated at values greater than 25 cm H_2O in adults and 28 cm H_2O in children when measured with patients in the left lateral decubitus position.[25-27]

CLINICAL FEATURES

Most patients with IIH present with one or more symptoms related to increased ICP. In the Idiopathic Intracranial Hypertension Treatment Trial, a randomized controlled trial that included 165 patients with IIH and mild vision loss, the most common presenting symptom was headache, followed by transient visual obscurations, back pain, pulse-synchronous tinnitus, dizziness, photophobia, neck pain including radicular pain, subjective visual loss, and diplopia (TABLE 4-3).[28] Although most patients with IIH have subacute or chronic symptoms, a subset of patients (fewer than 3%) may present with fulminant or malignant IIH and rapidly worsening visual loss over a few days, which should prompt emergent evaluation and aggressive management.[29]

KEY POINTS

- **Idiopathic intracranial hypertension (IIH) is a condition related to increased intracranial pressure (ICP) unexplained by another etiology.**
- **Secondary causes of elevated ICP that need to be excluded in cases of suspected IIH include but are not limited to brain tumor, neoplasm, venous sinus thrombosis, and infection.**
- **IIH decreases quality of life and may lead to blindness.**
- **IIH is most common in young women (15 to 44 years of age) who have a body mass index of 30 kg/m^2 or greater.**
- **Prevalence and incidence of IIH are increasing in adults and children along with obesity rates.**
- **Several metabolic conditions (eg, obesity, weight gain, polycystic ovarian syndrome, obstructive sleep apnea) are associated with IIH.**
- **IIH care may be delayed because of rural residence, limited transportation access, and health care costs.**
- **The risk of severe visual loss is higher in Black patients with IIH than in White, Hispanic, and Asian patients with IIH.**

Visual Symptoms and Ophthalmic Signs

Patients with IIH present with various visual symptoms.

TRANSIENT VISUAL OBSCURATIONS. Transient visual obscurations are short episodes, lasting seconds to minutes, of painless blurred vision, loss of vision, or graying out of vision that may be monocular or binocular and may occur multiple times a day. They are distinct from the visual aura related to migraines. Transient visual obscurations are commonly induced by sudden head or eye movement or after orthostatic positional changes, which may cause transient ischemia of the small, low-pressure vessels that supply the swollen optic nerve,[30] and occur less often in children than in adults (2% to 53% versus 72%).[31]

PAPILLEDEMA. Papilledema is the hallmark sign of IIH and is a term that is exclusively used when optic nerve swelling is secondary to increased ICP. Elevated intracranial subarachnoid CSF pressure leads to increased CSF pressure in the optic nerve sheath, which then increases tissue pressure in the optic nerve, leading to axoplasmic flow stasis and producing papilledema.[32] Papilledema is usually bilateral, but it may be asymmetric in 3% of patients with IIH.[33] Those with asymmetric papilledema are more likely to be asymptomatic, older, and have lower opening pressure on lumbar puncture.[33]

Severe papilledema may lead to vision loss; thus, examination of the ocular fundus is critical to evaluating any patient with relevant symptoms. Assessing the degree of papilledema allows for better risk stratification and guides the aggressiveness of treatment.[34] Neurologists can evaluate for papilledema at the bedside using a direct ophthalmoscope. A redesigned direct ophthalmoscope offers a wider field of view of the ocular fundus at 25 degrees, which is 5 times wider than a standard ophthalmoscope. Direct ophthalmoscopy may be limited because of its two-dimensional view, whereas indirect ophthalmoscopy performed with a slit lamp by an ophthalmologist or a neuro-ophthalmologist will provide a three-dimensional view to perceive depth or, in this case, elevation of the optic nerve. Tabletop and handheld nonmydriatic high-resolution digital fundus cameras or portable smartphone-based fundus cameras are increasingly available and allow immediate electronic transfer of imaging for remote interpretation by experts.[35]

TABLE 4-1

Modified Dandy Criteria for the Diagnosis of Idiopathic Intracranial Hypertension[a]

- **Signs and symptoms of increased intracranial pressure (eg, headaches, transient obscurations of vision, papilledema, pulse synchronous tinnitus, visual loss)**
- **No altered level of consciousness nor localizing neurologic signs, except unilateral or bilateral sixth nerve palsy**
- **Increased intracranial pressure with normal CSF composition**
- **Neuroimaging without any structural lesion or venous sinus thrombosis**
- **No other etiology explaining intracranial hypertension**

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[a] Reprinted with permission from Smith JL, J Clin Neuroophthalmol.[22] © 1985 Williams and Wilkins.

Papilledema severity can be rated using the modified Frisén grading scale, which was revised by identifying a key feature for each grade, whereas the other criteria were considered minor (**FIGURE 4-1**).[36] Frisén grade 0 is normal (no disc edema). Frisén grade 1 (minimal degree of edema) has a subtle and gray *C*-shaped halo that obscures the underlying retinal details but spares the temporal

Secondary Causes of Increased Intracranial Pressure[a]

TABLE 4-2

Medications

- Tetracycline, minocycline, doxycycline, fluoroquinolones
- Vitamin A and retinoids
- Growth hormone, levonorgestrel, anabolic steroids
- Withdrawal from chronic corticosteroids
- Lithium
- Methotrexate, cyclosporine, cytarabine hydrochloride, cytosine arabinoside
- Nalidixic acid

Medical conditions

- Anemia
- Addison disease
- Aldosteronism
- Behçet disease
- Down syndrome
- Hypervitaminosis A or hypovitaminosis A
- Hypoparathyroidism
- Leukemia
- Lyme disease
- Meningitis
- Sleep apnea
- Systemic lupus erythematosus
- Pickwickian syndrome
- Renal failure
- Turner syndrome

Intracranial abnormalities

- Cerebral venous outflow obstruction (eg, cerebral venous thrombosis, jugular vein thrombosis)
- Intracranial mass (eg, tumor, hemorrhage)
- Hydrocephalus
- Diffuse cerebral edema
- Chiari malformation

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[a] Data from Kilic K, et al, Cephalalgia.[23]

area. Frisén grade 2 (low degree of edema) has a complete circumferential halo. Frisén grade 3 (moderate degree of edema) has one or more major blood vessels obscured as it leaves the disc. Frisén grade 4 (marked degree of edema) has a major blood vessel obscured on the disc. Frisén grade 5 (severe degree of edema) has all vessels obscured on the disc and leaving the disc.

Retinal folds (ie, peripapillary wrinkles, retinal folds, and choroidal folds) may also be associated with papilledema (FIGURE 4-2[37]). In the Idiopathic Intracranial Hypertension Treatment Trial, at least 1 type of fold was seen in 41% of patients with photos and in 73% of patients with spectral domain optical coherence tomography (OCT).[37]

Retinal hemorrhages in the peripapillary or papillary retinal nerve fiber layer (FIGURE 4-3A and 4-3B) and cotton-wool spots (FIGURE 4-3A), which are focal retinal infarcts, may occur in association with papilledema. Increased ICP can compress the central retinal vein within the optic nerve sheath, which leads to venous outflow resistance and subsequent retinal hemorrhage and infarct. Some patients may also develop peripapillary exudates extending into the macula (ie, macular stars) (FIGURE 4-3C), which form as a result of a breakdown in the retinal capillary blood–inner retinal barrier leading to the formation of extravascular protein and lipid. Subretinal hemorrhage (FIGURE 4-3D) can also develop, which may occur from peripapillary subretinal neovascular membranes that rapidly evolve and then involute.[38]

Spontaneous venous pulsations are seen as subtle rhythmic changes in the retinal vein caliber across the optic disc synchronous with the cardiac cycle and are absent in patients with papilledema.[39] Spontaneous venous pulsations cease when the CSF pressure increases to greater than 19 cm H_2O.[40] Spontaneous

TABLE 4-3

Presenting Symptoms at the Time of Patient Enrollment in the Idiopathic Intracranial Hypertension Treatment Trial[a]

Presenting symptom	Prevalence, % (*N* = 165)
Headache	84
Transient visual obscurations	68
Pulsatile tinnitus	52
Back pain	52
Dizziness	51
Photophobia	48
Neck pain	42
Nonpulsatile tinnitus	23
Cognitive dysfunction	21
Radicular pain	19
Diplopia	18

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[a] Data from Wall, M, et al, JAMA Neurol.[28]

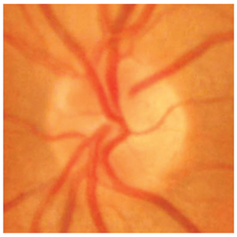
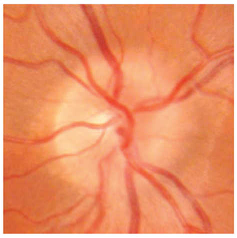
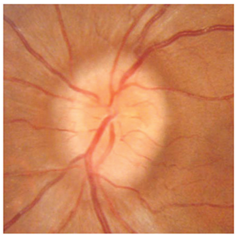
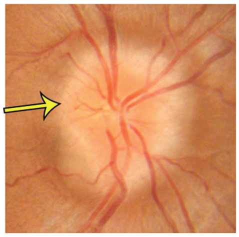
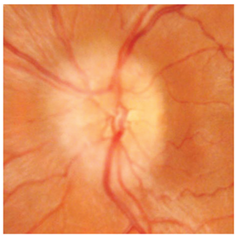
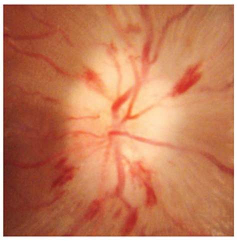
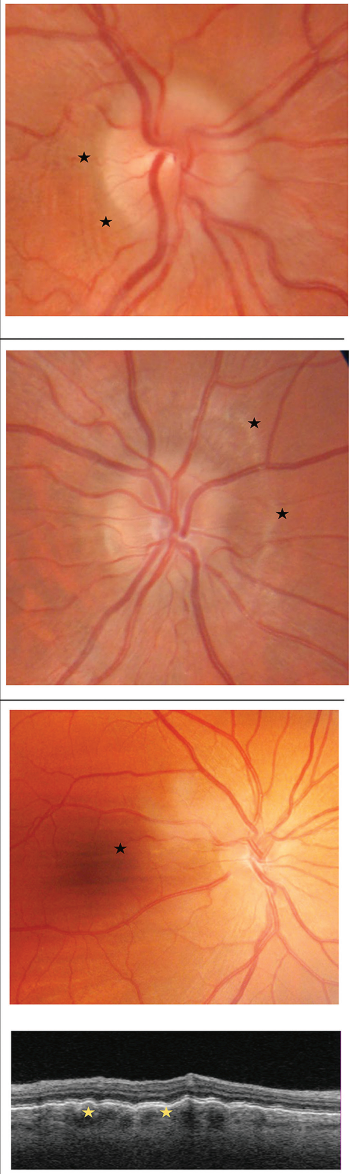
Papilledema grade	
0 (normal optic disc)	
1 (minimal degree of edema) Subtle and gray *C*-shaped halo, sparing the temporal area, that obscures underlying retinal details[a] Normal radial retinal nerve fiber layer arrangement striations disrupted Temporal disc margin normal	
2 (low degree of edema) Complete circumferential halo[a] Elevated nasal border No major vessel obscuration	
3 (moderate degree of edema) ≥1 major blood vessel obscured as it leaves the disc[a] (*yellow arrow*) Complete circumferential halo All borders elevated Halo: irregular outer fringe with fingerlike extensions	
4 (marked degree of edema) Major blood vessel obscured on the disc[a] Entire optic nerve head elevated, including the cup Complete border obscuration Halo: complete	
5 (severe degree of edema) All vessels obscured on the disc and leaving the disc[a]	

FIGURE 4-1

Modified Frisén grading scale.

[a] Major finding or key feature for papilledema grade.

Data from Scott CJ, Arch Ophthalmol.[36]



Peripapillary wrinkles
Periodic, alternating, fine, closely spaced folds (*stars*) on the disc surface or within half a disc diameter on the peripapillary retina

Retinal folds
Periodic surface or intraretinal undulations (*stars*) greater than half the disc diameter from the disc

Choroidal folds
Retinal folds (*stars*) associated with deep retinal pigment epithelial striations

FIGURE 4-2
Peripapillary wrinkles and retinal and choroidal folds associated with papilledema.
Data from Sibony PA, et al, Invest Ophthalmol Vis Sci.[37]

venous pulsations are present in 90% of individuals with normal ICP; thus, the absence of spontaneous venous pulsations does not necessarily confirm the diagnosis of increased ICP.

Papilledema should be differentiated from pseudopapilledema to prevent misdiagnosis of IIH, overutilization of health care resources, and undue anxiety for the patient. Pseudopapilledema is an elevation of the optic nerve head without retinal nerve fiber layer edema. Differentiating pseudopapilledema from papilledema is a frequent source of referrals to neuro-ophthalmology. A tilted optic disc is an oval-shaped optic disc that is elevated at its nasal aspect because the nerve enters the eye at an anomalous oblique angle (FIGURE 4-4A and 4-4B).

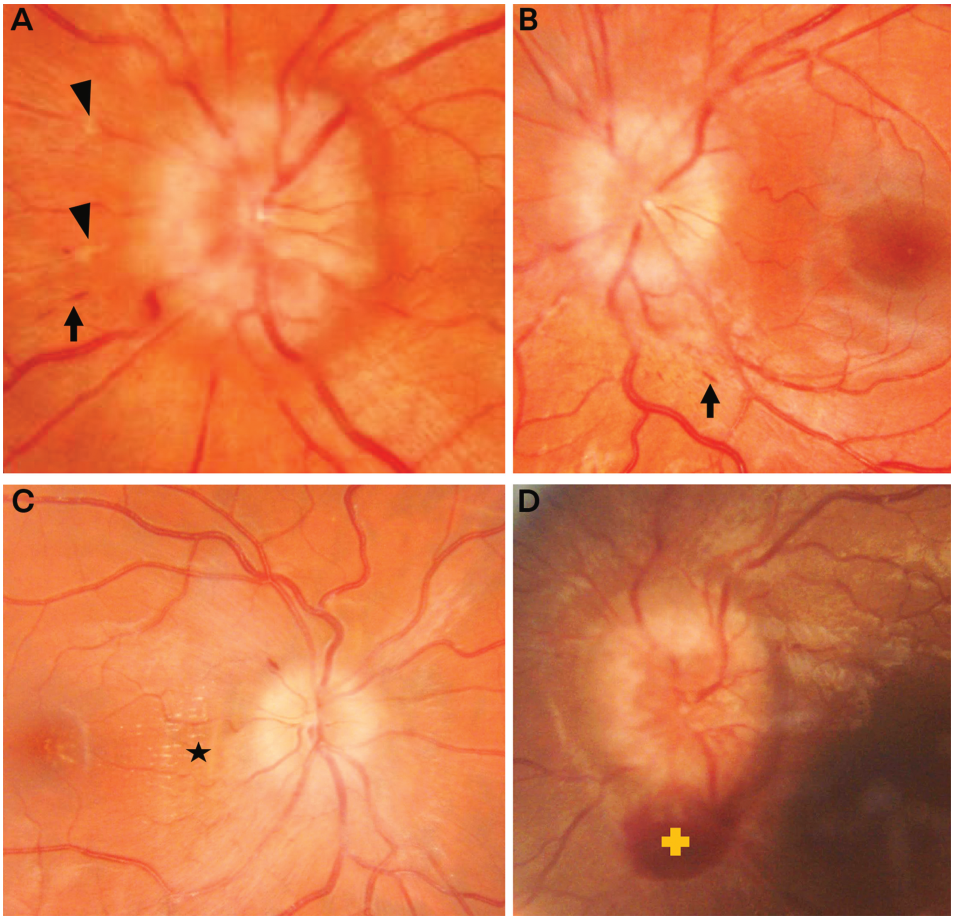


FIGURE 4-3
Additional ocular fundus findings that may be seen in association with papilledema. Retinal nerve fiber layer peripapillary hemorrhage (*A*, *B*, *arrows*), cotton wool spots (*A*, *arrowheads*), macular exudates (*C*, *star*), and subretinal hemorrhages (*D*, *yellow cross*).

Myelinated nerve fibers on the optic disc, which are secondary to anomalous migration of oligodendrocytes beyond the lamina cribrosa, may obscure the underlying disc and retina (FIGURE 4-4C). Optic disc drusen (FIGURE 4-4D), which are composed of calcium, mucopolysaccharides, and proteinaceous material, develop within the nerve and cause an elevated appearance of the optic disc head. Buried drusen are sometimes difficult to distinguish from true papilledema and may need further neuroimaging with CT of the orbits or with ocular imaging studies with B-mode ultrasonography of the eye. Drusen appear as hyperreflective structures within the optic nerve with acoustic shadowing on B-mode ultrasonography of the eye. Because drusen calcify over time, they appear as hyperdense lesions within the optic nerve head on orbital CT (FIGURE 4-4D).

MONITORING VISION AND PAPILLEDEMA. Direct or indirect ophthalmoscopy has traditionally been the method used for the crucial monitoring of papilledema, but some physicians may not be skilled or confident in performing this. Nondilated fundus photography can be a convenient, noninvasive monitoring tool.[41]

KEY POINTS

- **Direct medical and surgical hospital expenses contribute to the cost of care for patients with IIH, but half of the IIH burden of cost may be the result of lost wages and other nonmedical expenses.**
- **Transient visual obscurations are short episodes of painless loss of vision distinct from the visual aura related to migraines.**
- **Papilledema is the hallmark sign of IIH.**
- ***Papilledema* is a term used exclusively for optic nerve swelling due to increased ICP.**
- **Papilledema is usually bilateral but, rarely, may be asymmetric.**
- **Papilledema may lead to vision loss and is a risk-stratification tool guiding the clinician toward timely diagnosis and treatment.**
- **Visualization of the ocular fundus, either through funduscopy or fundus photography, is crucial in the diagnosis and monitoring of patients with IIH.**
- **Papilledema may be graded using the modified Frisén scale.**
- **The absence of spontaneous venous pulsations does not confirm the diagnosis of elevated ICP. Spontaneous venous pulsations are not seen in 10% of individuals with normal ICP.**

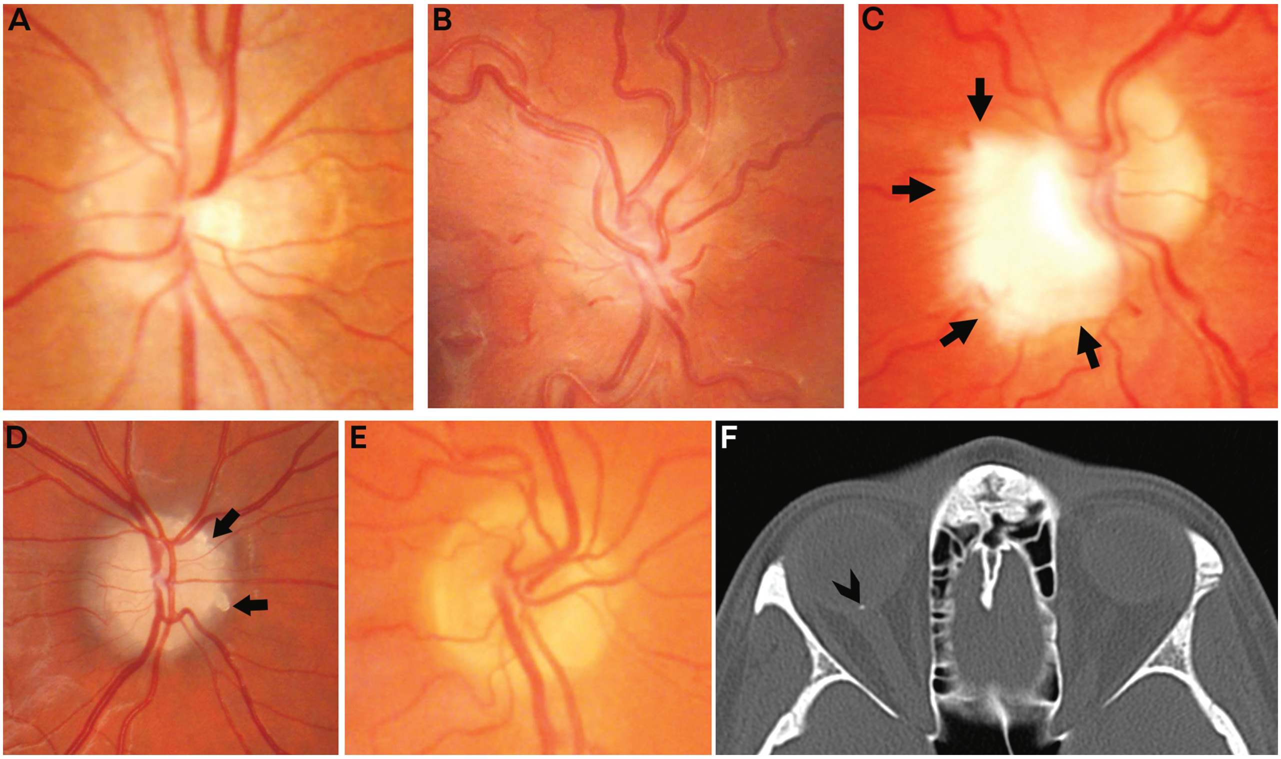


FIGURE 4-4

Pseudopapilledema. *A*, *B*, Tilted disc. *C*, Myelinated fibers on the optic disc (*arrows*). *D-F*, Optic disc drusen. Drusen visible at the optic disc (*D*, *arrows*). Elevated optic disc with a buried drusen (*E*) that is visible as a hyperdense lesion at the right optic disc head (*F*, *arrowhead*) on noncontrast CT of the orbits.

OCT is a noninvasive, noncontact, in vivo, readily available high-resolution imaging modality of the optic nerve and retina. The peripapillary retinal nerve fiber layer and the macular ganglion cell–inner plexiform layer thickness can be measured in microns. This allows the quantification of papilledema, which can play a role in monitoring patients with IIH. Monitoring papilledema with OCT retinal nerve fiber layer values alone is insufficient because of measurement variability, especially in the setting of severe papilledema.[42] OCT retinal nerve fiber layer thickness may be used in addition to formal visual field testing.

A decreasing OCT retinal nerve fiber layer thickness in a patient with IIH may reflect either success of therapy, with improving ICP control and subsequent papilledema improvement, or injury to the optic nerve causing retinal nerve fiber layer thinning secondary to axonal loss. The macular ganglion cell–inner plexiform layer thickness measured on the OCT may help distinguish retinal nerve fiber layer thinning from improving pressure control versus evolving damage to the optic nerve.[43,44]

VISUAL FIELDS. Serial visual field testing, along with evaluation of papilledema severity, is important in monitoring patients with IIH. Confrontation visual field testing may miss mild to moderate visual field loss[45]; thus, formal perimetry (eg, Humphrey, Goldmann, Octopus) is preferred in guiding IIH management.

At clinical presentation, 73% of the patients enrolled in the Idiopathic Intracranial Hypertension Treatment Trial had visual field abnormalities. The majority had localized nerve fiber bundle–type loss with an enlarged blind spot (**FIGURE 4-5A**) or without an enlarged blind spot (**FIGURE 4-5B**). Other visual field abnormalities seen were an enlarged blind spot without other nerve fiber bundle defects (**FIGURE 4-5C** and **4-5D**), diffuse loss, neurologic-like loss, and other abnormalities.[46] Most visual field changes involve the inferior hemifields. Central vision loss (**FIGURE 4-5E**) is rare, except in fulminant or malignant presentations. Central scotomas may occur when papilledema is severe and the edema spreads to the macula, causing serous detachment (**FIGURE 4-5E**).

DIPLOPIA AND SIXTH NERVE PALSY. Patients with IIH may also have episodic or constant binocular horizontal diplopia. Binocular diplopia resolves when covering or closing one eye. Double vision that is associated with elevated ICP is typically caused by sixth nerve palsy. It is usually initially noticed when the patient is looking at something distant and is worse on the affected side of lateral gaze. It can be unilateral or bilateral. Sixth nerve palsy manifests with limited abduction of the affected eye. Esophoria is worse on the affected side of lateral gaze and may be present in primary gaze or while the patient is looking straight ahead (**CASE 4-2**).

Sixth nerve palsy is not a precisely localizing sign. The abducens nerve is vulnerable as it travels along its comparatively long intracranial course in the subarachnoid space from the pons along the clivus (where it can be tethered) and to the orbit. Sixth nerve palsy occurs more often in children than adults (50% versus 20%) with IIH.[47]

OTHER VISUAL SYMPTOMS. Some patients with IIH may have nonspecific blurred vision or an enlarged blind spot related to a hyperopic shift related to disruption of the peripapillary fibers due to papilledema.[48] Metamorphopsia, a visual distortion wherein straight lines appear curved, occurs when increased ICP results in the flattening of the posterior globe or creation of papillomacular choroidal folds (**FIGURE 4-2**).[49]

Headache

Headache is the most common symptom of IIH in both adults and children, ranging from 78% to 95% across different studies.[50-52] IIH headache is classified by the International Classification of Headache Disorders, Third Edition, as a secondary headache disorder, wherein a new-onset headache or a significant worsening of a preexisting headache is caused by and accompanied by other symptoms and signs of IIH with a temporal relationship to increased ICP.[53] IIH headaches mimic primary headache disorders, including migraine and tension-type headache.[50] IIH-related headache pain can be throbbing, a pressure-like sensation, stabbing, or shooting. Associated symptoms include photophobia, phonophobia, osmophobia, nausea, emesis, and cutaneous allodynia. In the Idiopathic Intracranial Hypertension Treatment Trial, almost half of the patients had a previous history of migraine and were receiving medications to treat their headaches symptomatically.[50] The Idiopathic Intracranial Hypertension Treatment Trial and other studies have shown that headache negatively affects quality of life.[2] Notably, the Idiopathic Intracranial Hypertension Treatment Trial did not show any correlation between headache disability and CSF opening

KEY POINTS

- **Optical coherence tomography may be used in monitoring papilledema and IIH. Care should be taken in the interpretation of decreasing optical coherence tomographic retinal nerve fiber layer thickness because this may reflect either success of therapy or an evolving optic nerve injury.**
- **Mild to moderate vision loss may be missed on confrontation visual field testing; thus, formal perimetry is needed for monitoring patients with IIH.**
- **It is rare for a patient with IIH to present with central vision loss, except in a fulminant or malignant case. More commonly, a localized nerve fiber bundle defect, with or without an enlarged blind spot, is seen.**
- **Sixth nerve palsy is more common in children with IIH than in adults with IIH.**

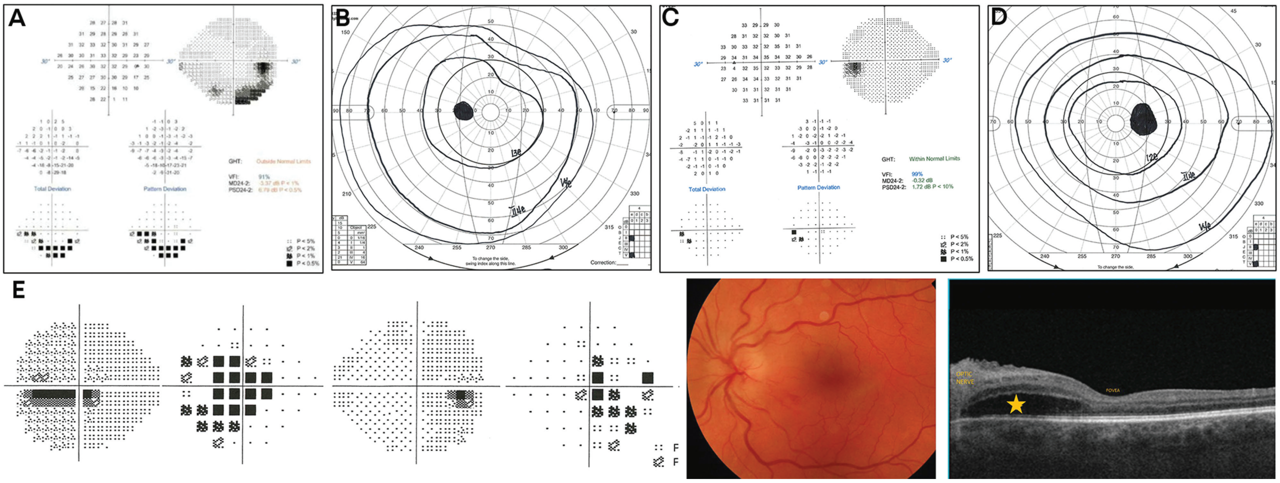


FIGURE 4-5

Visual field defects in idiopathic intracranial hypertension. Localized nerve fiber bundle-type loss with an enlarged blind spot of the right eye on Humphrey perimetry (*A*). Localized nerve fiber bundle-type loss without an enlarged blind spot of the left eye on Goldmann perimetry (*B*). An enlarged blind spot of the left eye on Humphrey perimetry (*C*) and of the right eye on Goldmann kinetic perimetry (*D*). Bilateral cecocentral scotoma on Humphrey perimetry (*E*) in a patient with fulminant idiopathic intracranial hypertension wherein the disc edema spread to the macular area causing serous detachment (*E*, *star*).

pressure at baseline,[50] but a more recent multicenter trial in the United Kingdom conversely showed that headache severity correlated with ICP at baseline.[52]

Neuro-otologic Symptoms

Patients with IIH may also present with neuro-otologic symptoms.

PULSATILE TINNITUS. Pulsatile tinnitus, or pulse-synchronous tinnitus, is a humming or whooshing sound that occurs with the heartbeat during the venous phase (diastole). In patients with IIH, the tinnitus may be unilateral or bilateral,

CASE 4-2

A 30-year-old woman presented to the emergency department because of double vision to which she attributed her nausea and worsening headaches. She was found to have bilateral sixth nerve palsy. Brain MRI and MR venography did not show any structural abnormalities. Opening pressure on lumbar puncture was elevated at 39 cm H_2O, with normal values of CSF components. She was diagnosed with idiopathic intracranial hypertension and discharged with acetazolamide. Hospital follow-up at the neuro-ophthalmology clinic showed not only the bilateral sixth nerve palsy but also bilateral papilledema. Humphrey perimetry revealed enlarged blind spots bilaterally.

COMMENT

This case highlights the importance of ocular funduscopy, as well as monitoring vision through formal visual field testing, in a patient with idiopathic intracranial hypertension.

episodic or constant. The exact pathophysiology of pulsatile tinnitus is unclear. It has been proposed that the vascular pulsations at the circle of Willis lead to fluid wave transmission through the CSF, which is then magnified in the setting of increased ICP. The pulsations then cause periodic compressions of the medial walls of the dural venous sinuses, leading to turbulent flow within these sinuses. Patients with IIH with pulsatile tinnitus were more likely to have increased BMI, larger pulse pressures, sleep apnea, and migraines.[54]

OTHER NEURO-OTOLOGIC SYMPTOMS. Patients with IIH may also experience dizziness. Elevated ICP may transmit compressive pressure on the cochleovestibular nerves or brainstem. Spontaneous skull base CSF leaks may present as rhinorrhea or otorrhea; for more information about this presentation, refer to the article "Atraumatic Cranial CSF Leaks" by Erin K. O'Brien, MD, and Maria Peris Celda, MD, PhD,[55] in this issue of *Continuum*. Other neuro-otologic manifestations include aural fullness, low-frequency sensorineural hearing loss, and phonosensitivity.[56,57]

Asymptomatic Presentation

IIH may be identified in the absence of any symptoms. The diagnosis of IIH was made after papilledema was incidentally seen on a routine eye evaluation in 10% to 48% of adult patients with IIH and in 22.6% of children with IIH.[58-60] Despite the lack of IIH symptoms, these patients can develop persistent papilledema, optic atrophy, or symptomatic disease.[61]

DIAGNOSTIC INVESTIGATIONS

IIH is a diagnosis of exclusion, and it is important to rule out secondary causes of increased ICP (CASE 4-3).

Neuroimaging

Along with a thorough neuro-ophthalmic assessment to confirm papilledema or sixth nerve palsy, urgent neuroimaging (MRI or CT with venogram) should be

CASE 4-3

A 62-year-old woman underwent her annual cataract evaluation and was incidentally found to have bilateral disc edema. She did not have any vision symptoms, headaches, or pulsatile tinnitus. Urgent workup showed a normal contrasted brain MRI and MR venogram. Lumbar puncture revealed an elevated opening pressure of 29 cm H_2O. CSF composition was normal, including cytology, except for an elevated protein of 106 mg/dL. MRI of her lumbar spine showed several lytic intraosseous lesions in the lumbar spine, sacrum, and iliac crest. In retrospect, she had been having lower back pain and some difficulty walking, which she had attributed to aging. Biopsy of one of these lesions confirmed multiple myeloma.

COMMENT

This case highlights the importance of excluding secondary causes of increased intracranial pressure, especially in the setting of an unusual demographic profile for idiopathic intracranial hypertension.

obtained to exclude secondary causes of elevated ICP. MRI without and with contrast is the preferred imaging modality in the setting of suspected IIH to exclude secondary causes of increased ICP (eg, intracranial space-occupying lesion, hydrocephalus, abnormal meningeal enhancement, venous sinus thrombosis).

Several findings on brain MRI have been associated with IIH, including empty sella, optic nerve sheath distention, optic nerve tortuosity, flattening of the posterior globe, optic nerve protrusion into the vitreous, and transverse venous sinus stenosis (FIGURE 4-6).[62] In isolation, these MRI findings do not show sufficient sensitivity or specificity for diagnosing IIH because they may also be present in patients without elevated ICP.[63,64] These MRI findings, if seen incidentally, without other signs or symptoms concerning for increased ICP, should not prompt invasive or costly investigations.[65]

Lumbar Puncture and CSF Studies

Lumbar puncture is the next diagnostic step after neuroimaging. Lumbar puncture has two purposes: (1) to confirm the presence of increased ICP by measuring the opening pressure and (2) to study the composition of the CSF to exclude secondary causes of elevated ICP. Opening pressure is ideally measured

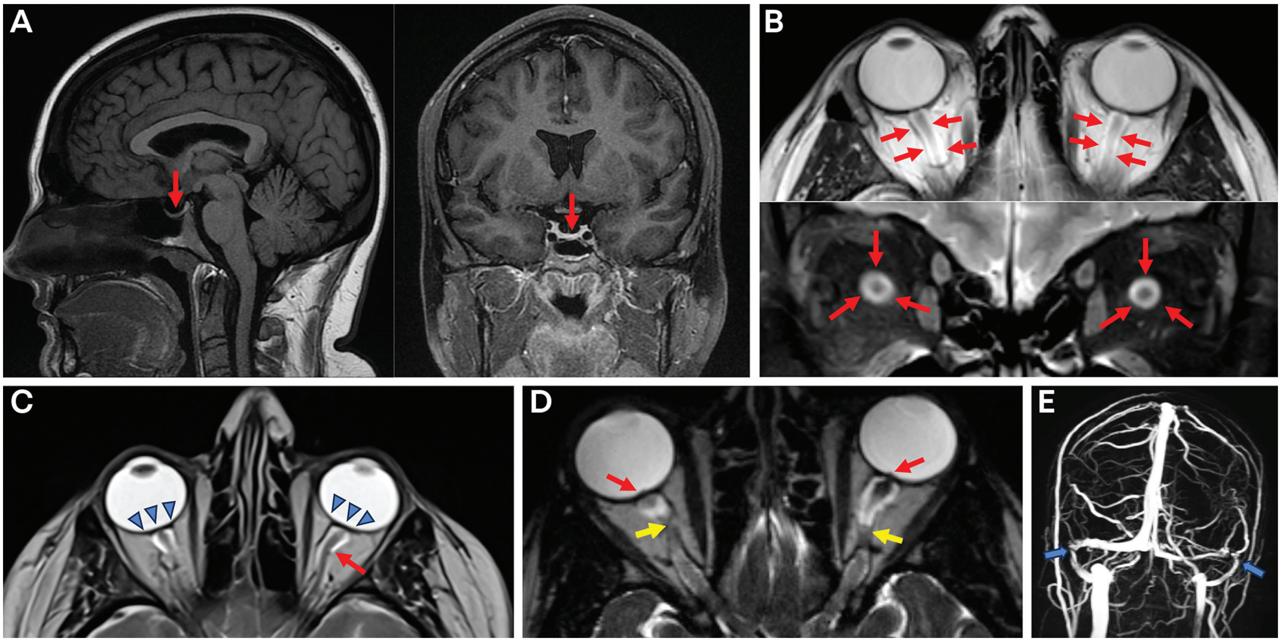


FIGURE 4-6

Subtle MRI findings associated with idiopathic intracranial hypertension. *A*, Empty sella. T1-weighted sagittal view (*left*) and T1-weighted postcontrast coronal view (*right*) showing the empty sella (*arrows*). *B*, Optic nerve sheath distention. T2-weighted axial view (*top*) and T2-weighted coronal view (*bottom*) showing bilateral distended optic nerve sheaths (*arrows*). *C*, Flattening of the posterior globe. T2-weighted axial view showing bilateral distended optic nerve sheaths, flattening of the posterior globes (*arrowheads*), and optic nerve tortuosity (*arrow*). *D*, Optic nerve tortuosity and optic nerve head protrusion into the vitreous. T2-weighted axial view showing the protrusion of the optic nerve into the posterior globe (*red arrows*) and the tortuous optic nerves with distended optic nerve sheaths (*yellow arrows*). *E*, Transverse venous sinus changes. Head MR venogram showing low-flow–related signal and heterogeneous diminished signal within the left transverse and bilateral sigmoid dural venous sinuses (*arrows*) consistent with dural venous sinus stenosis.

in the lateral decubitus position, with the patient as relaxed as possible, the legs extended, and the head in a neutral position. The 95% reference interval for lumbar CSF opening pressure is 10 to 25 cm H_2O[25,66,67]; thus, values greater than 25 cm H_2O are considered elevated for adults. In children, CSF opening pressure is considered elevated at greater than 28 cm H_2O.[27,68] Many children require sedation for a successful spinal tap, and caution must be taken in interpreting opening pressure because hypercapnia and hypoventilation, which may occur with sedation, might falsely elevate CSF pressure by increasing cerebral blood volume.[69]

Idiopathic Intracranial Hypertension Without Papilledema

Friedman and colleagues[70] revised the criteria for IIH to state that a diagnosis of IIH is suggested, but not confirmed in the absence of papilledema or sixth nerve palsy if the other modified Dandy criteria are met along with at least three typical neuroimaging findings (ie, empty sella, posterior globe flattening, perioptic subarachnoid space distention, transverse venous sinus stenosis). This clinical presentation is otherwise known as *IIH without papilledema*. A combination of any three of four MRI features was nearly 100% specific and 64% sensitive in 80 patients with IIH and papilledema. By using these criteria, IIH without papilledema was suggested in 30% of 33 patients with chronic headaches and elevated opening pressure (≥25 cm H_2O) but without papilledema.[71] A prospective study of patients undergoing brain MRI for any clinical indication showed that the same imaging criteria were 99% specific in identifying papilledema, with a sensitivity of only 20%.[72] Incidental findings on neuroimaging that have been associated with IIH are not diagnostic of IIH unless other signs of IIH, such as papilledema or sixth nerve palsy, are present.[73] Treatment trials for IIH have used the modified Dandy criteria and did not include patients who presented with IIH without papilledema.

It is unclear whether IIH without papilledema is pathophysiologically distinct from IIH, although they may be phenotypically similar.[74] Patients with IIH without papilledema have chronic headaches with increased ICP, but they generally do not experience vision loss. To avoid visual morbidity, it is important to monitor these patients longitudinally for possible delayed papilledema development.

Impact of Diagnostic Errors

Process failures in the workup of patients with IIH may lead to diagnosis failures, and errors made in the diagnosis may lead to inappropriate management with the potential for morbidity and death.[75,76]

In a retrospective study of 165 patients referred to the neuro-ophthalmology clinic with a diagnosis of IIH, overdiagnosis of IIH had occurred in 39.5% of patients because of diagnostic errors,[77] usually from the underuse of appropriate diagnostic tests, which led to unnecessary tests (overuse of diagnostic tests) and invasive procedures, potentially missing alternative diagnoses that required further investigations.[77,78] An example of underuse of diagnostic tests leading to IIH overdiagnosis is the inability to perform an accurate ocular fundus examination or by not performing ophthalmoscopy at all. Overuse of diagnostic tests is exemplified by relying on other weak criteria (eg, isolated radiologic findings possibly related to IIH, moderately elevated CSF opening pressure without papilledema or sixth nerve palsy). Anchoring to a unconscious bias (such

KEY POINTS

- **Patients with IIH may present asymptomatically, with papilledema incidentally discovered on routine eye evaluation.**
- **The preferred neuroimaging modality to exclude secondary causes of increased ICP is MRI without and with contrast, along with a CT or MR venogram.**
- **CSF opening pressure is considered elevated when it is greater than 25 cm H_2O for adults and greater than 28 cm H_2O for children measured in the left lateral decubitus position.**
- **Vision loss generally does not occur in patients with chronic headaches and elevated ICP without papilledema. It is important, though, to monitor these patients for possible delayed papilledema development.**

as thinking that women who are obese and have headaches must have IIH) may also lead to IIH overdiagnosis.[77] Strategies to reduce cognitive bias and diagnostic error must be implemented when faced with a patient who may have IIH because it is a diagnosis wherein assessment for secondary causes of elevated ICP may change the trajectory of management dramatically for these patients.[79]

CONCLUSION

IIH is a condition caused by elevated ICP of unknown etiology, commonly seen in women who are obese and of reproductive age. Papilledema is a hallmark sign of IIH, in the setting of a normal neurologic examination (except for sixth nerve palsy), neuroimaging excluding structural lesions and venous sinus thrombosis, and elevated opening pressure greater than 25 cm H_2O (>28 cm H_2O in children) with normal CSF composition. Accumulating data show that the increasing incidence and prevalence of IIH may relate to health disparities that have an impact on the neurologic and whole-person care of these patients.

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REVIEW ARTICLE

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Treatment and Monitoring of Idiopathic Intracranial Hypertension

By John J. Chen, MD, PhD; Susan P. Mollan, MBChB, PhD, FRCOphth

ABSTRACT

OBJECTIVE: This article reviews the management of idiopathic intracranial hypertension (IIH), which is essential to neurology practice.

LATEST DEVELOPMENTS: The incidence and prevalence of IIH have risen because of the worldwide obesity epidemic. Evidence suggests that IIH has a unique systemic metabolic phenotype. Clinical history, examination, and visual fields remain the cornerstone for monitoring people with IIH. Optical coherence tomography demonstrates structural changes that aid decision-making. The principles of IIH management include protecting vision and escalating to surgical interventions when it is threatened, addressing the role of obesity in the condition, and providing advice on headache therapeutics. There are no labeled therapies for IIH; however, acetazolamide remains the most common medication prescribed. A glucagon-like peptide-1 receptor agonist was recently shown to reduce intracranial pressure independent of weight reduction in a phase II randomized controlled trial in people with IIH, suggesting it could be a promising treatment for IIH. In patients with IIH requiring surgery, there has been an increase in venous sinus stenting.

ESSENTIAL POINTS: Neurologists are central in the management pathway for people with IIH. Ongoing coordinated care between ophthalmologists and neurologists is essential for optimal care of these patients.

INTRODUCTION

Idiopathic intracranial hypertension (IIH), a condition of increased intracranial pressure (ICP), occurs most commonly in young women with obesity, typically with a body mass index (BMI) greater than 30 kg/m^2. Although it is principally associated with obesity, there are also specific systemic metabolic findings in people with IIH.[1] The incidence of the disease is increasing in line with obesity rates.[2] IIH causes debilitating headaches and, in some, visual loss. It negatively affects quality of life, reduces the capacity to work, and makes performing activities of daily living difficult.[3,4] People with IIH have been found to have impaired fertility, gestational diabetes, preeclampsia, increased risk of cardiometabolic complications, and reversible cognitive dysfunction.[5-7] Disease associations include obstructive sleep apnea (OSA), polycystic ovarian syndrome, and mental health disorders.[8-12]

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RELATIONSHIP DISCLOSURE:
Dr Chen has received personal compensation in the range of $500 to $4999 for serving as a consultant for Amgen Inc and in the range of $5000 to $9999 for serving as a consultant for UCB S.A. Dr Mollan has received personal compensation in the range of $0 to $499 for serving on speakers bureaus for Teva Pharmaceutical Industries Ltd and Thea Pharma Inc and in the range of $500 to $4999 for serving as a consultant for Invex Therapeutics. The institution of Dr Mollan has received research support from the National Institute for Health Research.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Chen and Mollan discuss the unlabeled use of acetazolamide, glucagon-like peptide 1 receptor agonists, and topiramate for the treatment of idiopathic intracranial hypertension.

IIH used to be termed *benign intracranial hypertension*, but the disease can cause progressive and insidious vision loss, which is typically reversible with treatment but has been reported to be permanent in up to 40% of cases.[13,14] The visual defects are most often in the periphery, not appreciated by the patient until it is advanced; therefore, monitoring visual function with serial examinations and visual fields is essential. Optical coherence tomography (OCT) has become indispensable in monitoring the structure of the optic nerve.

The course of disease is variable.[15] For some, IIH symptoms and signs will resolve after a single diagnostic lumbar puncture and weight loss. In a minority of patients with IIH, incipient visual loss needs to be aggressively managed with a surgical procedure such as CSF diversion, optic nerve sheath fenestration, or venous sinus stenting.[16,17] For most patients with IIH, medical management, such as acetazolamide, and weight loss are appropriate.[18] Elevated BMI is the main modifiable risk factor, but it is highly stigmatized, and there are many barriers to management.[19] Headache after normalization of ICP remains an unmet clinical need that requires active management for most patients.[20]

MONITORING IDIOPATHIC INTRACRANIAL HYPERTENSION

Regular assessment of visual function and optic nerve head imaging is necessary to identify patients at risk of visual loss because headache frequency and severity of papilledema are not correlated (TABLE 5-1). Because body weight change is the major modifiable risk factor for IIH disease activity, calculating the BMI should be part of every routine follow-up assessment. Headache burden should be methodically tracked to provide evidence of a response to treatment.

Tests of Visual Function at Diagnosis and Follow-up

Visual acuity should be measured in each eye separately. The best method for checking high-contrast visual acuity is a distance-illuminated chart at 6 meters (20 feet). Patients should wear their corrective eyeglasses or contact lenses. If their vision is not 20/20, it should be rechecked with a pinhole, which can eliminate refractive error. Papilledema often causes a hypermetropic shift that may affect the distance vision mildly but can be corrected with a pinhole. A moderate to severe reduction of visual acuity is a serious sign that may occur early in aggressive disease, likely the result of fluid tracking toward the macula, or late in chronic papilledema because of optic neuropathy.[21] Acquired dyschromatopsia is a key sign that the papilledema is threatening vision. Color vision is usually assessed in the eye clinic with pseudoisochromatic color plates (TABLE 5-1). A pupil examination is essential to detect a relative afferent pupillary defect or sluggish pupils. Eye movement examination may determine if sixth nerve palsy is present (TABLE 5-1).

Visual field testing must be performed on every patient with IIH. Serial visual fields over time are important to monitor visual function. Visual field testing to confrontation is a gross test and insensitive in detecting early visual field defects, so formal visual fields should be sought at the earliest opportunity (TABLE 5-1). Any type of visual field defect can be found in papilledema, the most common are enlargement of the blind spot, followed by an inferior nasal step (partial arcuate defect), and then generalized depression of the visual field (peripheral constriction) (FIGURE 5-1).[22]

In clinical practice, automated perimetry is routinely used because it provides the visual field sensitivity (including the mean deviation) (TABLE 5-1).[23] Visual

KEY POINTS

- Testing visual function is important in patients with idiopathic intracranial hypertension (IIH) as there is no correlation between headache frequency and severity of papilledema.
- Repeat assessments of body mass index (BMI) should be made in patients with IIH to determine long-term weight trajectory and effectiveness of weight management treatment.
- A higher grade of papilledema and more significant loss in visual acuity at presentation are associated with a higher risk of progression to permanent visual field loss.
- High-contrast visual acuity (such as Snellen acuity), visual evoked potentials, and confrontational visual field are not sensitive enough methods to detect the visual loss associated with papilledema. All patients with IIH and papilledema should be followed with formal perimetry.
- The visual field dysfunction in patients with IIH can affect the full visual field but increases with eccentricity (ie, occurs more in the periphery).
- Goldmann visual fields, a form of manual perimetry, are helpful for patients with IIH who have attention difficulties and fatigue.
- If the perimetry is not consistent with the rest of the visual assessment, it should be interpreted cautiously, as functional visual loss can occur in patients with IIH.

TABLE 5-1 Recommended Visual Monitoring in Patients With Idiopathic Intracranial Hypertension With Papilledema

Visual acuity

- High contrast visual acuity is tested using a distance-illuminated chart at 6 meters (20 feet), which may not be available in the emergency department or inpatient hospital setting. A near card held at 36 centimeters (14 inches) is a convenient alternative.
- Visual acuity should not be used in isolation because it is not sensitive to detect the early visual loss caused by papilledema. Rapidly declining visual acuity occurs with severe optic nerve ischemia and should be urgently evaluated.

Color vision

- Color vision is typically evaluated with pseudoisochromatic plates, with abnormal color vision indicating optic nerve dysfunction. These tools may not be readily available at the bedside. An alternative is using objects of color or red pins and assessing the subjective brightness of colors compared between eyes or across the vertical meridian of one eye. Dyschromatopsia in the setting of papilledema is a serious sign.

Pupil examination

- A relative afferent pupillary defect may be seen if there is asymmetrical papilledema and vision loss. Sluggish pupils may be present in patients with severe papilledema and significant vision loss.

Eye movements

- A unilateral or bilateral sixth nerve palsy may be noted. This finding may be subtle, as indicated by a far-distance esotropia on cover testing, or more apparent, as a frank esotropia and limitation of abduction. Horizontal fast eye movements (saccades) will be affected if there is a sixth nerve palsy.

Visual fields to confrontation

- Confrontational visual fields are insensitive to pick up visual field loss from papilledema unless the vision is severely affected. To test visual fields by confrontation, the examiner sits roughly 1 meter away from the patient and asks the patient to cover one eye and look at the examiner's opposite pupil. The patient must identify the number of fingers presented within each quadrant. Red and white pins can then be used to assess the central 30°, exploring for any scotoma or enlarged blind spot.

Formal visual fields

- Formal visual fields are most commonly assessed with automated perimetry.
- For example, the Humphrey visual field 24-2 tests 24° temporally and 30° nasally at 54 preselected points. Most automated perimetry tests have a threshold test in which steps of 4 dB are used until detected, then retested at every point in 2-dB steps.
- An unreliable field may reflect poor technique and may improve with familiarization or changing to an alternative test (eg, Goldmann perimetry).

Fundus examination

- Fundoscopy documents optic nerve head and macula findings and excludes ocular causes of disc swelling.

Optical coherence tomography

- This technique tracks optic nerve head and macula ganglion cell layer measurements and evaluates for retinal pathology.

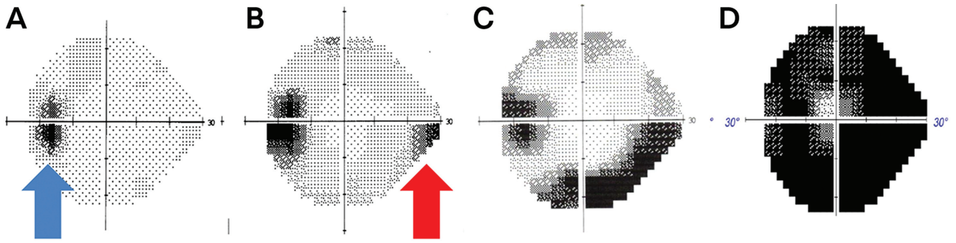


FIGURE 5-1
Visual field defects of varying severity that occur in the setting of idiopathic intracranial hypertension. The first visual field defect to manifest with papilledema is enlargement of the blind spot (*A*, *blue arrow*), followed by nasal step (*B*, *red arrow*), arcuate defects (*C*), then generalized constriction (*D*).

field testing is dependent on technician and patient performance, and results can vary.[24,25] The learning effect can be mitigated by offering patients multiple attempts to allow for familiarization.[24] In the Idiopathic Intracranial Hypertension Treatment Trial, up to one in five patients had a performance failure at one visit.[25] Reliability indices are essential to review to determine the quality of the test. A high prevalence of functional vision loss has been reported in people with IIH, which may affect visual field performance (FIGURE 5-2).[26] Cognitive deficits have been shown in people with active IIH, and reduction in reaction time and processing speed can influence the visual field results.[7,27]

Papilledema Monitoring

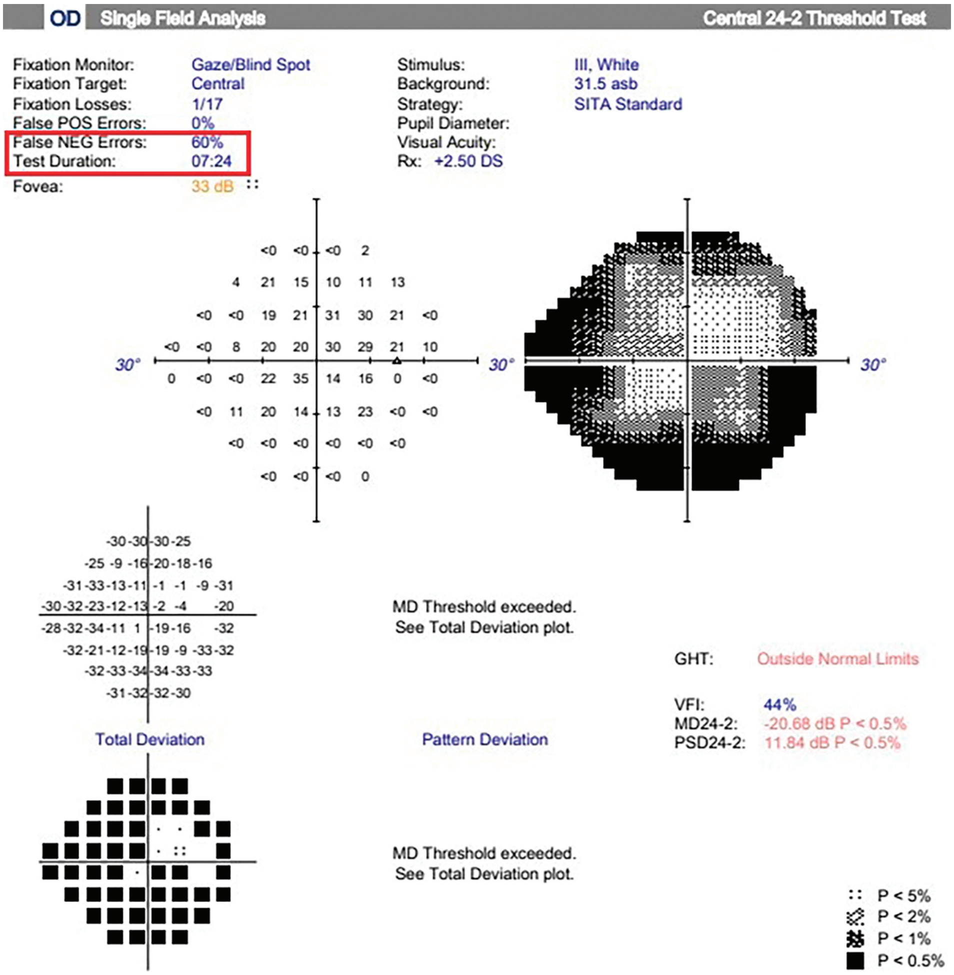
Change in papilledema can be formally graded using the Frisén classification on a dilated slit-lamp examination or by fundus photographs.[28] Clinical practice has shifted to using OCT, a noninvasive, light-based imaging technique that enables in vivo, high-resolution, cross-sectional imaging of structures. OCT provides both qualitative and objective quantification of papilledema that facilitates long-term monitoring and is the most sensitive test for changes in papilledema (FIGURE 5-3 and VIDEOS 5-1, 5-2, and 5-3).[29] OCT cross-sectional and *en face* imaging can detect outer retinal changes such as subretinal fluid, peripapillary wrinkles, inner retinal folds, outer retinal folds and creases, and choroidal folds.[21,30]

The OCT peripapillary retinal nerve fiber layer, the most common measurement reported, has been found to better quantify papilledema than the traditional Frisén grading because it provides a continuous scale.[28] The Frisén grading scale is less reliable after treatment compared with OCT optic nerve head volume.[31] Although it can be difficult to determine if a reduction in measurements is the result of a reduction in edema or optic atrophy, studies have shown that the magnitude of change in moderate to severe papilledema is correlated with treatment.[15,32] A methodical approach to reviewing OCT images should be adopted, particularly to check the automated segmentation for errors that can occur at higher degrees of papilledema.[33,34] Research continues to provide evidence of OCT measurements correlating with ICP.[35-39]

There is emerging evidence for a structure-function correlation between measurements of the optic nerve head, macular ganglion cell layer, and the visual field. Peripapillary retinal nerve fiber layer thickness abnormalities in mild papilledema are quantitatively correlated with visual field loss.[40] OCT macular ganglion cell layer measurements can help to predict the functional disability

KEY POINTS

- **All patients with IIH with papilledema should have serial examinations of the fundus, preferably documented with either photographs or optical coherence tomography imaging.**
- **Optical coherence tomography of the optic nerve head is the most sensitive test for changes in papilledema.**
- **In the setting of moderate to severe papilledema, the automated segmentation of optical coherence tomography images is often erroneous and may require manual correction.**
- **Central to the care of a person with IIH is a sensitive discussion about the role of body weight and its association with IIH.**
- **Dietary approaches, creating an energy deficit of 500 to 1000 cal/d, may be effective in the short term (up to 6 months) for modest weight loss in patients with IIH.**
- **A multicomponent intervention (diet, physical activity, and behavior) may be effective in the short term (up to 6 months) for modest weight loss in patients with IIH, but weight loss may not be maintained in the longer term (ie, longer than 24 months).**
- **A low-salt diet can lead to temporary body weight reduction because of body water reductions, but this approach does not change body fat and has not proven to be beneficial in the setting of IIH.**



OD Single Field Analysis

Central 24-2 Threshold Test

Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 1/17
False POS Errors: 0%
False NEG Errors: 60%
Test Duration: 07:24
Fovea: 33 dB

Stimulus: III, White
Background: 31.5 asb
Strategy: SITA Standard
Pupil Diameter:
Visual Acuity:
Rx: +2.50 DS

MD Threshold exceeded.
See Total Deviation plot.

GHT: Outside Normal Limits

VFI: 44%
MD24-2: -20.68 dB P < 0.5%
PSD24-2: 11.84 dB P < 0.5%

MD Threshold exceeded.
See Total Deviation plot.

<0 <0 <0 2
4 21 15 10 11 13
<0 <0 19 21 31 30 21 <0
<0 <0 8 20 20 30 29 21 10
30°
30°
0 <0 <0 22 35 14 16 0 <0
<0 11 20 14 13 23 <0 <0
<0 <0 <0 <0 <0 <0
<0 <0 <0 0
30°
30°
-30 -30 -30 -25
-25 -9 -16 -20 -18 -16
-31 -33 -13 -11 -1 -1 -9 -31
-30 -32 -23 -12 -13 -2 -4 -20
-28 -32 -34 -11 1 -19 -16 -32
-32 -21 -12 -19 -19 -9 -33 -32
-32 -33 -34 -34 -33 -33
-31 -32 -32 -30
Total Deviation
Pattern Deviation
P < 5%
P < 2%
P < 1%
P < 0.5%

FIGURE 5-2

Humphrey visual field with a bitemporal hemianopia clover-leaf pattern and high false-negative errors. This Humphrey visual field printout is an example of an unreliable visual field in a person with idiopathic intracranial hypertension. The gray scale shows a cover-leaf pattern. The false-negative errors are recorded at 60%, and the test duration is longer than 5 minutes (*red box*).

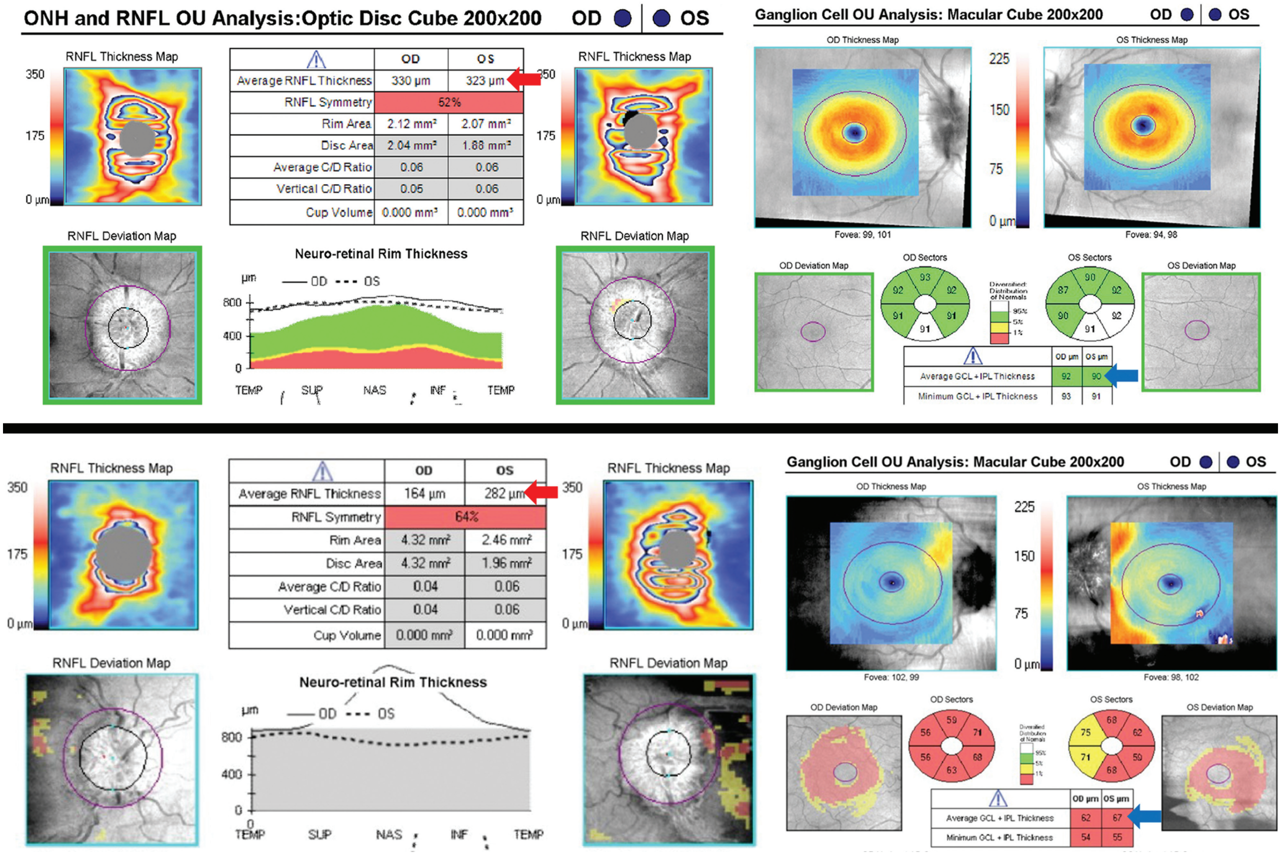
caused by papilledema.[21,37,41] In addition, macular ganglion cell layer measurements help determine if a decrease in peripapillary retinal nerve fiber layer thickness is the result of an improvement in the papilledema or worsening optic atrophy. In the former, the macular ganglion cell layer thickness will remain stable, whereas the latter will result in a decrease in both peripapillary retinal nerve fiber layer and macular ganglion cell layer thickness (**FIGURE 5-3**).

DISEASE-MODIFYING TREATMENT OF IDIOPATHIC INTRACRANIAL HYPERTENSION

The aggressiveness of treatment of IIH largely depends on the degree of papilledema and vision loss. See **FIGURE 5-4** for an algorithmic treatment approach to IIH.

The Role of Obesity

Obesity is a complex chronic relapsing disease. The population risk of developing IIH increases exponentially in those with a BMI greater than 30 kg/m^2.[6] An



ONH and RNFL OU Analysis:Optic Disc Cube 200x200
OD
OS
RNFL Thickness Map
350
175
0 µm
RNFL Deviation Map
Neuro-retinal Rim Thickness
µm
OD
OS
800
400
0
TEMP
SUP
NAS
INF
TEMP
Ganglion Cell OU Analysis: Macular Cube 200x200
OD Thickness Map
OS Thickness Map
225
150
75
0 µm
Fovea: 99, 101
Fovea: 94, 98
OD Deviation Map
OD Sectors
93
92
92
91
91
91
Diversified Distribution of Normals
95%
5%
1%
OS Sectors
90
87
92
90
92
91
OS Deviation Map

⚠	OD	OS
Average RNFL Thickness	330 µm	323 µm
RNFL Symmetry	52%	
Rim Area	2.12 mm²	2.07 mm²
Disc Area	2.04 mm²	1.88 mm²
Average C/D Ratio	0.06	0.06
Vertical C/D Ratio	0.05	0.06
Cup Volume	0.000 mm³	0.000 mm³

⚠	OD µm	OS µm
Average GCL + IPL Thickness	92	90
Minimum GCL + IPL Thickness	93	91

RNFL Thickness Map
350
175
0 µm
RNFL Deviation Map
Neuro-retinal Rim Thickness
µm
OD
OS
800
400
0
TEMP
SUP
NAS
INF
TEMP
Ganglion Cell OU Analysis: Macular Cube 200x200
OD
OS
OD Thickness Map
OS Thickness Map
225
150
75
0 µm
Fovea: 102, 99
Fovea: 98, 102
OD Deviation Map
OD Sectors
59
56
71
56
68
63
Diversified Distribution of Normals
95%
5%
1%
OS Sectors
68
75
62
71
59
68
OS Deviation Map

⚠	OD	OS
Average RNFL Thickness	164 µm	282 µm
RNFL Symmetry	64%	
Rim Area	4.32 mm²	2.46 mm²
Disc Area	4.32 mm²	1.96 mm²
Average C/D Ratio	0.04	0.06
Vertical C/D Ratio	0.04	0.06
Cup Volume	0.000 mm³	0.000 mm³

⚠	OD µm	OS µm
Average GCL + IPL Thickness	62	67
Minimum GCL + IPL Thickness	54	55

FIGURE 5-3

Optical coherence tomography (OCT) peripapillary retinal nerve fiber layer (RNFL) quantification and macular ganglion cell layer analysis in the setting of idiopathic intracranial hypertension (IIH). The OCT readouts are color-coded: white is too thick (>95% compared with age-matched controls), green is normal (5-95% compared with age-matched controls), yellow is borderline thin (1-5% compared with age-matched controls), and red is very thin (<1% compared with age-matched controls). *Upper row*: The OCT shows a severely thickened peripapillary retinal nerve fiber layer (*red arrow*) consistent with grade 3-4 papilledema but intact macular ganglion cell layer thickness (*blue arrow*) indicative of preserved optic nerve integrity. This patient with IIH could potentially be treated with medication. *Lower row*: The OCT shows a thickened peripapillary retinal nerve fiber layer (*red arrow*) consistent with grade 3 papilledema, but the macular ganglion cell layer thickness is thin (*blue arrow*), indicating that there is a combination of both papilledema and optic nerve atrophy. This patient with IIH requires aggressive treatment.

OD = right eye; ONH = optic nerve head; OS = left eye.

individual's weight threshold to develop IIH is not clear, and body weight is not a reliable indicator of visceral adiposity. Weight gain of 5% to 15% carries a risk for both developing and experiencing a recurrence of IIH.[42] There is increasing awareness that IIH is a systemic metabolic disorder.[1,43] Adipose distribution is preferentially centripetal and has been shown to correlate with ICP changes in IIH.[44] Adipocytes are transcriptionally and metabolically primed for lipogenesis and weight gain.[45] The central adiposity actively secretes mineralocorticoid-releasing factors, which could be another possible mechanism of increased ICP.[44] Weight-loss methods have evolved, and several studies have demonstrated a good correlation between weight loss and disease remission.[46]

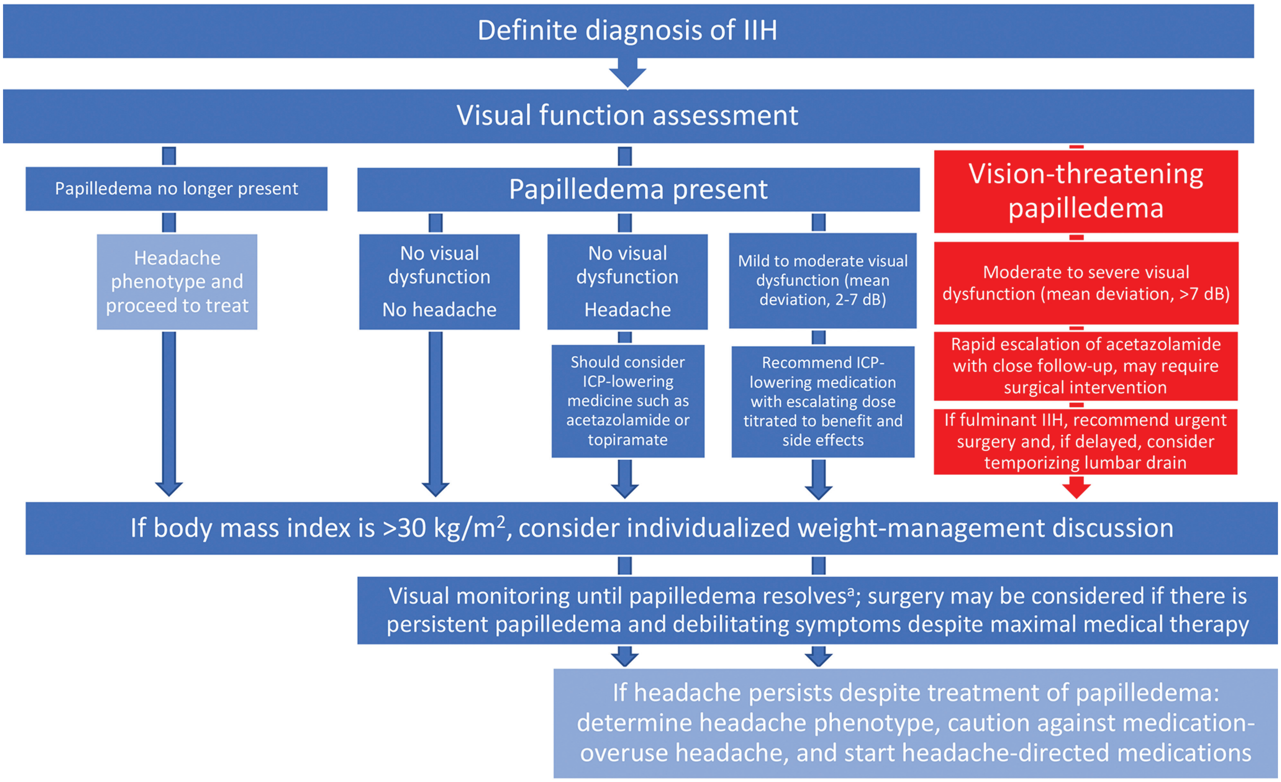

Definite diagnosis of IIH
Visual function assessment
Papilledema no longer present
Papilledema present
Vision-threatening papilledema
Headache phenotype and proceed to treat
No visual dysfunction
No headache
No visual dysfunction
Headache
Mild to moderate visual dysfunction (mean deviation, 2-7 dB)
Moderate to severe visual dysfunction (mean deviation, >7 dB)
Should consider ICP-lowering medicine such as acetazolamide or topiramate
Recommend ICP-lowering medication with escalating dose titrated to benefit and side effects
Rapid escalation of acetazolamide with close follow-up, may require surgical intervention
If fulminant IIH, recommend urgent surgery and, if delayed, consider temporizing lumbar drain
If body mass index is >30 kg/m², consider individualized weight-management discussion
Visual monitoring until papilledema resolvesª; surgery may be considered if there is persistent papilledema and debilitating symptoms despite maximal medical therapy
If headache persists despite treatment of papilledema: determine headache phenotype, caution against medication-overuse headache, and start headache-directed medications

FIGURE 5-4

Treatment algorithm for idiopathic intracranial hypertension (IIH) based on visual function.

ICP = intracranial pressure.

[a] Recommend closer monitoring in patients with higher degrees of papilledema or visual dysfunction.

There is increasing awareness of the stigma of obesity, and people often experience negative emotions when recalling discussions regarding weight management.[19] There are several recommendations for communicating this sensitive subject, including asking permission to discuss body shape and providing evidence of the role of weight changes in the occurrence of IIH.[19]

Weight-loss Methods

As weight change correlates with IIH disease activity, weight and height measurements should be taken to calculate BMI at each visit. This approach helps determine the long-term weight trajectory and effectiveness of weight-management interventions.[19,46] Self-reported weight has been shown to be inaccurate.[47,48]

Lifestyle Interventions

Lifestyle changes are most commonly recommended because they can be effective for weight loss,[48] and access to weight management services in many health care settings is limited. These changes include very-low-energy diets alone or in combination with group behavioral therapy and physical activity. Dietary approaches, creating an energy deficit of 500 to 1000 cal/d, may be effective in the short term (up to 6 months) for modest weight loss in patients with IIH. A low-salt diet is often recommended specifically for patients with IIH, but the evidence supporting this is minimal. Low-salt diets may change body weight through reduced extracellular water and total body water but have little impact on body fat mass, visceral fat area, or skeletal muscle mass.[49] Hence, low-salt diets are not recommended for weight-loss interventions alone.[46] A crossover study evaluated a very-low-calorie diet in the setting of IIH, which resulted in significantly lowered ICP, improved papilledema, and a 50% improvement in headache frequency and severity, with a concomitant reduction in analgesic use.[50] The major drawback of low-energy diets is that one-third to one-half of weight lost is regained at 1 year, and many return to their original (prediet) body weight within 5 years.[51]

Anti-obesity Medications

Historically, weight-loss medications such as orlistat achieved a little more weight loss than the lifestyle intervention alone.[51] Carbonic anhydrase inhibitors (eg, acetazolamide, topiramate, zonisamide) have previously been observed to

Known Side Effects of the Glucagon-like Peptide 1 Receptor Agonists TABLE 5-2

Common[a]

- Nausea and vomiting
- Stomach pain
- Headache
- Fatigue
- Dizziness
- Constipation or diarrhea
- Heartburn, indigestion, or gastroesophageal reflux disease
- Low blood sugar in people with type 2 diabetes
- Bloating, belching, and flatulence
- Mood changes
- Drug interactions

Uncommon short and intermediate term[b,c]

- Allergic reaction (anaphylaxis)
- Acute pancreatitis
- Acute cholelithiasis (gallstones)
- Acute kidney injury
- Diabetic retinopathy in people with type 2 diabetes
- Changes in heart rate
- Suicidal behavior or ideation
- Risk of thyroid C-cell tumors
- Gastroparesis
- Bowel obstruction

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[a] Common is defined as 1 in 10 to 1 in 100 (1-10%).
[b] Uncommon is defined as 1 in 101 to 1 in 1000 (0.1-1%).
[c] It is yet to be confirmed whether there is a rare risk of nonarteritic ischemic optic neuropathy associated with use of glucagon-like peptide 1 receptor agonists.

reduce weight, but they are not recommended anti-obesity drugs. In the Idiopathic Intracranial Hypertension Treatment Trial, the acetazolamide and multicomponent weight-management intervention group lost more weight than those in the placebo arm who had the same multicomponent weight-management intervention.[18] Weight loss is likely caused by the side effects of dysgeusia (ie, a salty, rancid, or metallic taste), nausea, dyspepsia, vomiting, and diarrhea.

Glucagon-like peptide 1 (GLP-1) receptor agonists are routinely used in the setting of type 2 diabetes and obesity without diabetes.[52] GLP-1 is a gut neuropeptide secreted by the distal small intestine in response to a meal.[53] GLP-1 stimulates glucose-dependent insulin secretion and reduces glucagon release, thereby lowering blood glucose without causing hypoglycemia.[54] It slows gastrointestinal motility and increases satiety. Longer-acting GLP-1 receptor agonists tend to promote better weight loss and glycemic control. Gastrointestinal side effects can resolve by 8 weeks of therapy but are a major reason approximately 12% of patients discontinue the medicines (**TABLE 5-2**). Importantly in adults who are overweight or obese without diabetes, treatment with GLP-1 receptor agonists reduced the risk of cardiovascular events[55,56]; this finding is of particular interest in the setting of IIH given the adverse cardiovascular outcomes that have been found in these patients.[6] An open-label study in people with IIH evaluated GLP-1 receptor agonists alongside usual-care weight management and found significant weight loss, improved headache outcomes at 6 months of treatment, and reduced requirement for acetazolamide.[57] A key area that requires consideration in the setting of IIH is the rebound weight gain experienced after cessation of GLP-1 receptor agonists, which could risk disease relapse.

For sustained weight loss, bariatric surgery is the most effective option. The Idiopathic Intracranial Hypertension Weight Trial compared bariatric surgery to a community weight-management program and found that ICP was significantly lower in the bariatric surgery arm at 12 months (adjusted mean difference, -6.0 cm H_2O) and reduced further at 24 months (adjusted mean difference, -8.2 cm H_2O).[58] The degree of weight loss was significantly associated with the reduction in ICP, and a mean weight loss of 13.3 kg (29.3 lb) was associated with disease remission, defined as lumbar puncture opening pressure less than 25 cm H_2O.[58] Bariatric surgery has known complications (eg, surgical complications, gastric ulcers, strictures, adhesions, internal hernia, depression, and maladaptive eating) and many long-term health benefits (eg, reduced or improved type 2 diabetes, cardiovascular disease, OSA, depression, and fertility). The upfront costs are high, but cost-effectiveness occurs over time.[59,60] In the Idiopathic Intracranial Hypertension Weight Trial, a 24% weight loss was effective in achieving remission, and this was demonstrated to be not achievable without bariatric surgery. The Roux-en-Y bypass performed the best in reduced ICP and weight loss.[61] At 2 weeks after surgery, those who underwent Roux-en-Y bypass had a 50% greater reduction in ICP compared with those who had a gastric sleeve procedure. Meal stimulation suggested that this occurred by enhanced GLP-1 secretion in the Roux-en-Y bypass group.[62] The 5-year results of the Idiopathic Intracranial Hypertension Weight Trial[63] confirmed the sustainability of bariatric surgery. Because of the potential serious complications with bariatric surgery, patients require prescreening with a multidisciplinary team, including a dietitian, endocrinologist, surgeon, and psychologist, before proceeding with surgery.[64]

MEDICAL TREATMENTS FOR IDIOPATHIC INTRACRANIAL HYPERTENSION

There are several medications used to treat increased ICP in patients with IIH, including acetazolamide and topiramate. GLP-1 receptor agonists are a promising class of medications.

Acetazolamide

Acetazolamide, a carbonic anhydrase inhibitor, is the most commonly used treatment for IIH and reduces ICP through modulating CSF secretion potentially by inhibiting the sodium-potassium ATPase pump and increasing aquaporin-1 in the choroid plexus.[65,66] Acetazolamide was confirmed to be effective in the Idiopathic Intracranial Hypertension Treatment Trial; this was a prospective multicenter, randomized, double-masked, placebo-controlled study that compared acetazolamide and multicomponent weight-management intervention (low-sodium, reduced-energy diet alongside behavioral support and physical activity recommendations) against placebo and multicomponent weight-management intervention.[18] The Idiopathic Intracranial Hypertension Treatment Trial enrolled 165 patients with IIH with mild vision loss (mean deviation between -2 db and -7 dB). At 6 months, participants who were randomly assigned to receive acetazolamide had a larger improvement in visual fields, papilledema, and vision-related quality of life.[18,67] There was no difference between treatment arms in improvement in headache. A subset of patients underwent repeat lumbar puncture, which showed acetazolamide was associated with a larger reduction in opening pressure compared with placebo.[67] Although the acetazolamide group had more weight loss than the placebo group, acetazolamide was reported to have a significant benefit even after controlling for its effect on weight loss.[18]

The typical starting dose of acetazolamide for IIH is either 250 mg 2 times a day or 500 mg 2 times a day, which can be escalated up to 4000 mg/d in patients with more severe papilledema. The Idiopathic Intracranial Hypertension Treatment Trial demonstrated that 44% of participants tolerated the maximum allowed dosage of acetazolamide of 4000 mg/d. Only 10% of participants discontinued acetazolamide, two because of pregnancy.[68] Common side effects were paresthesia, dysgeusia, diarrhea, nausea, and fatigue, which were significantly higher with acetazolamide than placebo. Aplastic anemia was not seen in the trial, and periodic monitoring of complete blood cell counts was not felt to be necessary or cost-effective.[68-70] Clinically significant hypokalemia was also not seen, and routine monitoring of potassium or supplementation is not typically necessary unless the patient is on a concomitant diuretic.[68,70] Although urolithiasis did not occur at a higher rate in the acetazolamide group compared with the placebo group in the Idiopathic Intracranial Hypertension Treatment Trial, this complication is a known potential risk that can be seen with acetazolamide with longer treatment.[68,71] Although acetazolamide is a sulfonamide agent, it has a different moiety than sulfa antibiotics, and therefore, a sulfa allergy is not considered a contraindication to using acetazolamide.[72]

Topiramate

Topiramate, a medication with mild carbonic anhydrase inhibition activity, may be beneficial in the setting of IIH through several mechanisms: direct action at the choroid plexus to reduce ICP and its propensity to induce weight loss.[73] In addition, topiramate can treat migraine headaches, which is a common

KEY POINTS

- **Glucagon-like peptide 1 receptor agonist drugs approved for weight management may be useful in the immediate management of patients with IIH requiring weight loss.**
- **If glucagon-like peptide 1 receptor agonist drugs are only used in the short-term in the setting of IIH, patients should be counseled that weight regain is likely once the medication is stopped.**
- **Evidence supports the use of acetazolamide with a multicomponent weight-management intervention for modest improvements in visual function in patients with mild visual loss from IIH.**
- **Counseling patients about the side effects of acetazolamide can improve adherence to treatment in patients with IIH.**
- **Although acetazolamide is a sulfonamide agent, it has a different moiety than sulfa antibiotics, and therefore, a sulfa allergy is not considered a contraindication to using acetazolamide.**

comorbidity in patients with IIH.[74,75] An open-label study of 40 patients with IIH comparing topiramate and acetazolamide showed an equivalent improvement in papilledema grade, with the topiramate group having significantly more weight loss than the acetazolamide group.[76] In a rodent model, topiramate led to a significant reduction in ICP whereas other medications, including acetazolamide, did not.[77] Changing the administration route from subcutaneous to oral, however, showed that both topiramate and acetazolamide led to a significant reduction in ICP within 120 minutes of administration.[78]

Topiramate is typically started at 25 mg once daily and increased by 25 mg every couple of weeks to 100 mg 2 times a day according to benefits and tolerability. Topiramate can cause cognitive slowing and depression, two comorbidities often present in patients with IIH,[79,80] which can limit its utility in some patients. In addition to reducing the effectiveness of oral contraceptives, topiramate is teratogenic and, therefore, contraindicated in pregnancy. Topiramate can rarely cause renal stones or angle closure glaucoma.

Glucagon-like Peptide 1 Receptor Agonists

GLP-1 receptor agonists have many systemic effects, including signaling at the hypothalamus to regulate satiety and sodium reabsorption and promoting diuresis through action in the renal proximal tubule.[81] GLP-1 receptors are also expressed in the choroid plexus, and GLP-1 receptor agonism reduced CSF secretion and ICP in an in vivo rodent model with elevated ICP.[82] The reduction in ICP was of a greater magnitude than that observed with other agents with unlabeled use to reduce ICP in vivo.[77] This discovery was translated into the IIH: Pressure trial that evaluated exenatide, a GLP-1 receptor agonist, in people with active IIH.[83] The study used telemetric ICP devices to avoid serial lumbar punctures.[84] This small trial found a clinically meaningful reduction in ICP at 2.5 hours, 24 hours, and 12 weeks in the exenatide arm compared with the placebo group. At the final follow-up at 12 weeks, there was no significant change in the BMI in the exenatide arm, indicating that the reduction of ICP was not driven by the change in body weight but by a direct drug effect in modulating ICP. Common side effects of GLP-1 receptor agonists include nausea and vomiting, but they can also cause more serious adverse effects, including pancreatitis, gastroparesis, and bowel obstruction.[85]

Other Medications

Other medicines that have been used as unlabeled treatment for IIH include furosemide (20 mg 2 times a day to 40 mg 2 times a day), methazolamide (75 mg 2 times a day to 150 mg 2 times a day), octreotide, spironolactone, and amiloride. Furosemide is a loop diuretic, and evidence for its use exists in other conditions of raised ICP.[86] Furosemide is thought to inhibit the sodium-potassium-chloride cotransporter on choroid plexus epithelial cells, and in animal studies, it reduces CSF secretion by 20% to 50%.[87] Methazolamide, another carbonic anhydrase inhibitor, is sometimes used in patients who do not tolerate acetazolamide. Octreotide is a synthetic somatostatin analogue. Because somatostatin receptors are highly expressed in the arachnoid villi and choroid plexus, it was postulated that octreotide could directly influence CSF dynamics. Two studies have documented improvement in IIH symptoms, but this may be mediated by the drug's anti-obesity properties.[88,89] Spironolactone is a potassium-sparing diuretic, and its effect on orthostatic (dependent) edema along with chlorthalidone and sympathomimetic therapy has been assessed in patients with IIH and matched control groups. Although no formal ICP outcomes were recorded, some patients reported reduced headaches and were documented to have reductions in papilledema.[90] A crossover trial in women with telemetric ICP monitors demonstrated that acetazolamide, furosemide, spironolactone, and topiramate all significantly reduced ICP, while amiloride had no significant effect.[91,92]

SURGICAL TREATMENTS FOR IDIOPATHIC INTRACRANIAL HYPERTENSION

The initial mainstay of treatment for IIH is weight loss and medical therapy, but surgical treatment is indicated in the setting of fulminant IIH and when all avenues of medical therapy have been exhausted. In up to 10% of patients, IIH will not be controlled by medications and may require surgery.[91] Surgical options include CSF diversion procedures, optic nerve sheath fenestration, venous sinus stenting, and bariatric surgery. The selection of surgery is currently based on the surgical experience of the institution and providers, although some surgeries may be favored in certain scenarios. Serial lumbar punctures are not a long-term option because the decreases in ICP are very short lived and the lumbar puncture opening pressure does not correlate with visual loss or guide management. As there are currently no head-to-head comparative trials, the efficacy and complications of surgeries are largely based on large case series and observational studies.

CSF Diversion Procedures (Shunts)

CSF diversion procedures historically have been the most common surgical procedure for treating IIH. These procedures lower ICP by diverting CSF from the ventricles in the brain into an alternative cavity in the body, typically via a lumboperitoneal or ventriculoperitoneal shunt. There has been a shift toward ventriculoperitoneal shunts over lumboperitoneal shunts because the latter have a higher risk of failure and need for revision.[93] A large systematic review of surgical procedures for IIH reported an improvement in papilledema, visual fields, and headaches in 78.9%, 66.8%, and 69.8%, respectively, of the patients treated with CSF diversion techniques.[94] Studies limited to ventriculoperitoneal shunt showed regression of papilledema in 90.9%; however, severe complications occurred in 9.4% and shunt failure in 43.4% of patients.[94] The median time to shunt failure has been reported to be 22.9 months.[95] Complications include infection, migration of the tubing, obstruction, and CSF overdrainage.[96] Although shunting is associated with a rapid decrease in CSF pressure and papilledema, because of the higher rates of complications and failure, there has been a shift toward reserving CSF diversion techniques for cases of more severe vision-threatening papilledema.

Optic Nerve Sheath Fenestration

During optic nerve sheath fenestration, a slit or window is made in the dural sheath of the optic nerve, which may reduce papilledema by allowing filtration of CSF into the subarachnoid space or by creating scarring at the surgical site to prevent further accumulation of CSF at the optic nerve head.[97] A large meta-analysis of surgical procedures for IIH showed optic nerve sheath fenestration led to improvement in papilledema in 90.5% of patients, whereas headaches improved in only 49.3%.[94] Complications include pupillary dysfunction, diplopia

KEY POINTS

- **There is no requirement for repeated measurements of CSF pressure in patients with IIH because the lumbar puncture opening pressure does not correlate with visual loss or guide management.**
- **Ventriculoperitoneal shunts lead to regression of papilledema in 90.9% of patients with IIH, but severe complications occurred in 9.4% and shunt failure in 43.4% of patients.**
- **Optic nerve sheath fenestration leads to an improvement of papilledema in 90.5% of patients, but headaches improved in only 49.3%.**

(typically transient and most associated with a medial transconjunctival approach), traumatic optic neuropathy, and ischemic complications, including central retinal artery occlusion.[98] Although mild complications were reported to occur in 20% of patients, the more serious complications, such as iatrogenic vision loss or diplopia requiring strabismus surgery, occurred in only 2.2%. The pooled analysis of optic nerve sheath fenestration cases showed that 16.9% required an additional surgical procedure, such as shunting or venous sinus stenting.[94]

Because optic nerve sheath fenestration has a favorable safety profile without risk of complications to the brain, it is a useful option for patients with

CASE 5-1

A 27-year-old woman with a body mass index (BMI) of 35 kg/m^2 presented to the eye clinic with headaches, pulsatile tinnitus, and transient visual obscurations. She was found to have grade 4 papilledema with mild choroidal folds. Her visual acuity was 20/30 in both eyes but refracted to 20/20 with a hyperopic shift. Visual field testing showed significant enlargement of the blind spots (FIGURE 5-5 and FIGURE 5-6). MRI and MR venography showed no abnormalities other than indirect signs of raised intracranial pressure, including bilateral transverse sinus stenosis (FIGURE 5-7). Lumbar puncture showed an elevated opening pressure of 57 cm H_2O with normal CSF composition. She was diagnosed with idiopathic intracranial hypertension and started on acetazolamide 500 mg 2 times a day, which was quickly escalated to 2000 mg 2 times a day because of the severity of the papilledema. Weight loss was encouraged. She was closely monitored initially every 1 to 2 weeks on high-dose acetazolamide, and the papilledema improved to grade 3 at 6 weeks and grade 2 at 3 months (FIGURE 5-5). Although she had also lost 9 kg (20 lb), she developed kidney stones and, therefore, had to stop the acetazolamide, resulting in the worsening of papilledema back to grade 4. Surgical options were discussed, and she underwent venous sinus stenting of the right transverse sinus and had resolution of pulsatile tinnitus and improvement in headaches (FIGURE 5-7). She was placed on clopidogrel and aspirin after the stenting procedure. Follow-up at 3 months demonstrated an improvement to grade 1 papilledema (FIGURES 5-5, 5-6, and 5-7). A CT venogram showed a patent stent in the right transverse sinus. Clopidogrel was stopped, and she was continued on aspirin 81 mg daily for 1 year.

COMMENT

Patients with severe papilledema but mostly intact visual fields can be initially treated with medical therapy provided they have close surveillance with serial visual fields and optical coherence tomography to monitor for worsening optic neuropathy. If maximum tolerated medications fail to improve papilledema, the patient may be a candidate for a surgical procedure. Venous sinus stenting can be effective in lowering intracranial pressure and improving papilledema. After venous sinus stenting, patients are typically placed on dual antiplatelet therapy for 3 months, followed by aspirin monotherapy for at least 1 year.

vision-threatening papilledema who do not have a large headache component. Although some patients require bilateral optic nerve sheath fenestration, unilateral optic nerve sheath fenestration often causes a reduction in papilledema in the contralateral eye.[99]

Venous Sinus Stenting

More than 90% of patients with IIH have bilateral transverse sinus stenosis, typically at the junction of the transverse and sigmoid sinuses,[100] which has led to the speculation that venous outflow could play a role in the pathogenesis of IIH.[101,102] Venus sinus stenting was first described for IIH in 2002,[103] and it has

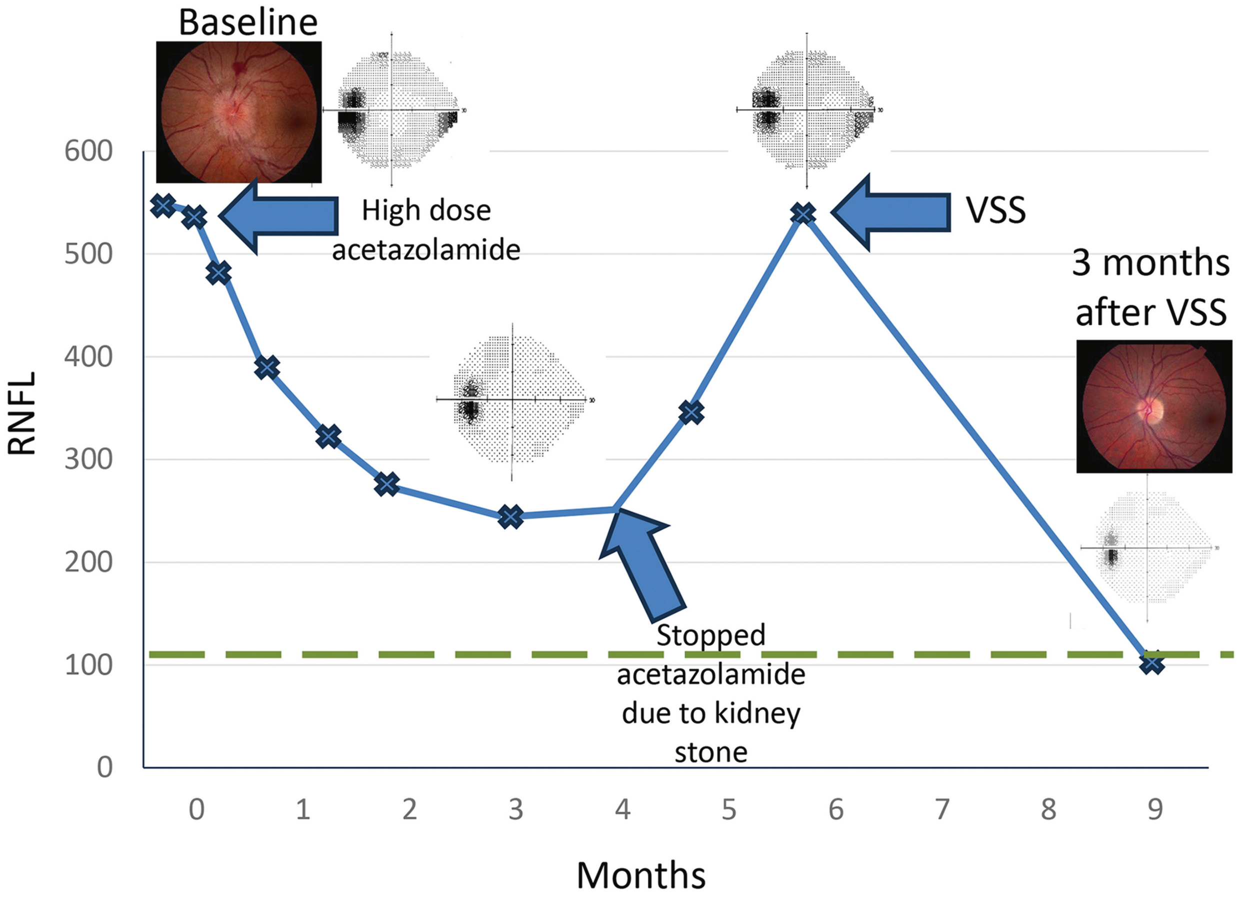

FIGURE 5-5

Clinical course of the patient in CASE 5-1 who has idiopathic intracranial hypertension. The retinal nerve fiber layer (RNFL) thickness at each clinic visit is marked with a *blue X*. The *green dashed line* shows a normal RNFL at approximately 100 μm for healthy young individuals.

VSS = venus sinus stenting.

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CASE 5-1

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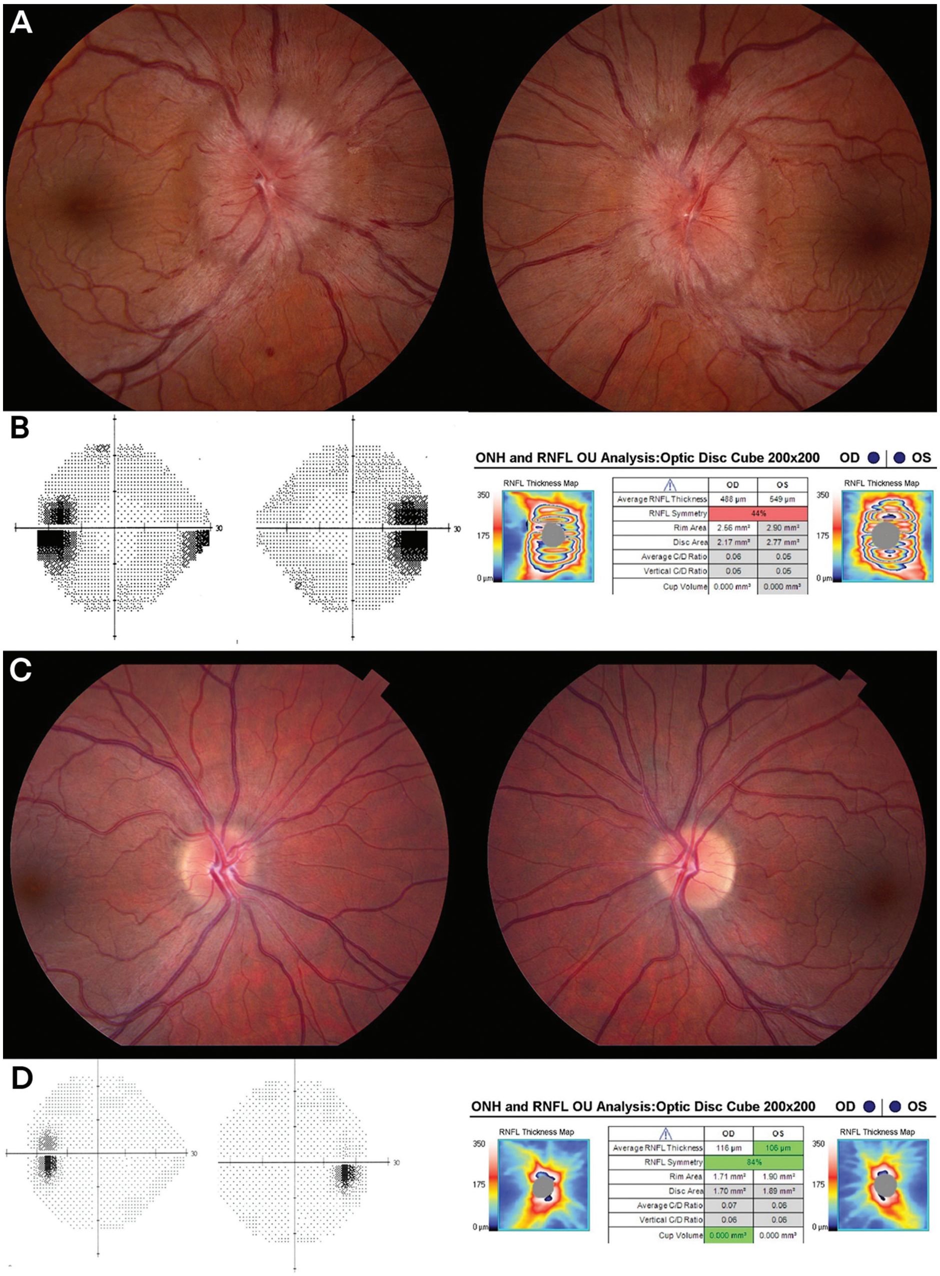
A
B
30
30
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● | ● OS
RNFL Thickness Map
350
175
0 µm
RNFL Thickness Map
350
175
0 µm
C
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30
30
ONH and RNFL OU Analysis:Optic Disc Cube 200x200 OD ● | ● OS
RNFL Thickness Map
350
175
0 µm
RNFL Thickness Map
350
175
0 µm

⚠	OD	OS
Average RNFL Thickness	488 µm	549 µm
RNFL Symmetry	44%	
Rim Area	2.56 mm²	2.90 mm²
Disc Area	2.17 mm²	2.77 mm²
Average C/D Ratio	0.06	0.05
Vertical C/D Ratio	0.05	0.05
Cup Volume	0.000 mm³	0.000 mm³

⚠	OD	OS
Average RNFL Thickness	116 µm	106 µm
RNFL Symmetry	84%	
Rim Area	1.71 mm²	1.90 mm²
Disc Area	1.70 mm²	1.89 mm²
Average C/D Ratio	0.07	0.06
Vertical C/D Ratio	0.06	0.06
Cup Volume	0.000 mm³	0.000 mm³

FIGURE 5-6

Optical coherence tomography and visual field testing from the patient in CASE 5-1. Fundus photographs (*A*) show grade 4 papilledema, optical coherence tomography and visual fields (*B*) show significantly thickened peripapillary retinal nerve fiber layer (RNFL) and enlargement of the blind spots, respectively, before venous sinus stenting. Three months after venous sinus stenting, fundus photographs (*C*) show significant improvement in the papilledema to grade 1 and significant reduction in the peripapillary retinal nerve fiber layer, and visual fields (*D*) show the reduction in the size of the blind spots.

OD = right eye; ONH = optic nerve head; OS = left eye; OU = both eyes.

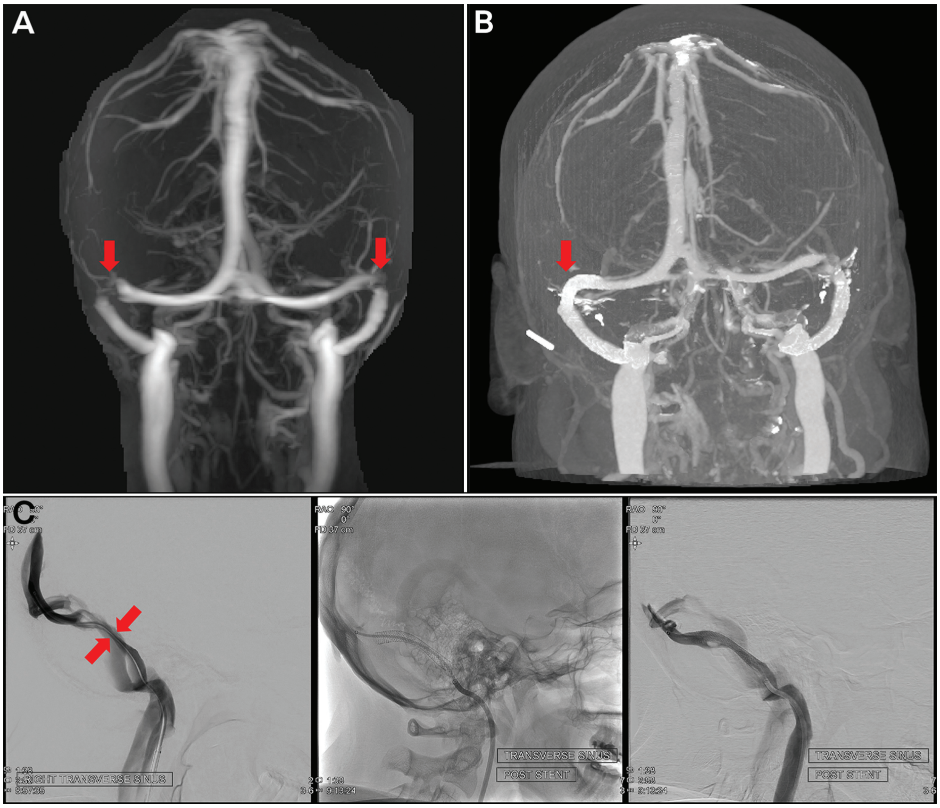


FIGURE 5-7
Imaging findings from the patient in CASE 5-1. *A*, An MR venogram shows bilateral transverse venous sinus stenosis before venous sinus stenting (*arrows*). *B*, A CT venogram shows the right venous sinus stent (*arrow*). *C*, During the venous sinus stent procedure, a microcatheter is introduced into the venous system, usually through the femoral or internal jugular vein, which is then navigated through the jugular vein and into the dural venous sinus. Contrast is then administered to confirm the presence and location of the stenosis (*arrows*). A pressure transducer attached to the microcatheter is used to measure the gradient across the stenosis, which was 14 mm Hg in this patient. After stent placement, venography and manometry are repeated to confirm resolution of the stenosis and improvement in the pressure gradient.

become increasingly used for the treatment of medication-refractory IIH over the past decade.[101,104] A 2023 study using the National Inpatient Sample database showed that venous sinus stenting increased by 80% from 2016 to 2020, whereas CSF shunting and optic nerve sheath fenestration decreased by 19% and 54%, respectively, over the same period.[101] A meta-analysis comparing outcomes and complications of surgical procedures for IIH suggested that venous sinus stenting outcomes are similar or better than optic nerve sheath fenestration and shunting procedures.[105] Papilledema usually improves after venous sinus stenting, but 9% of patients require an additional surgical procedure, and severe adverse events occur in 2.3% of cases, which include thrombosis, stent migration, subdural or intradural hematoma, subarachnoid hemorrhage, and obstructive hydrocephalus.

During the venous sinus stenting procedure, the pressure gradient across the stenosis is measured to confirm hemodynamically significant stenosis (**CASE 5-1**).

Most proceduralists require at least an 8-mm Hg gradient before deploying a self-expanding stent across the stenosis, although some studies suggest that treating a gradient as low as 4 mm Hg can have beneficial effects.[106] To decrease the risk of in-stent thrombosis, most patients are pretreated with dual antiplatelet therapy, given heparin during the procedure, and continued on dual antiplatelet therapy for a short period after venous sinus stenting, typically 3 months, followed by aspirin for at least 1 year (some indefinitely).[106]

In a 2018 venous sinus stenting meta-analysis of 1626 patients, 719 patients had an average prestent opening pressure of 33 cm H_2O, and 250 patients had a mean drop of 13.3 cm H_2O after the stenting procedure.[102] Pulsatile tinnitus resolved in the majority.[102,107] Headaches improvement was variable with rates ranging from 48% to 92% reported.[101,102] Resolution or improvement in papilledema after venous sinus stenting ranged from 63% to 100%.[101,102,108-110] Pooled complication rates have been reported at 9.4%.[94] Most are mild complications, such as hematoma at the femoral access site. Headaches ipsilateral to the side of the venous sinus stenting lasting hours to weeks after the procedure are common and likely related to stretching of the dura. More severe adverse events occur in 2.3% of patients, which include thrombosis, stent migration, subdural or intradural hematoma, subarachnoid hemorrhage, obstructive hydrocephalus, and even death.[94] The serious complication of cerebral hemorrhage has been reported in 0.5% to 1% of patients.[94,101,102] A large meta-analysis reported that 9% of patients required an additional surgical procedure for continued symptoms of increased ICP, most commonly a second stenting procedure, but also shunting procedures and bariatric surgery.[102] One study reported the reoperation rate as high as 25.9%.[111] Future prospective randomized clinical trials are required to determine the true efficacy and complication rates of venous sinus stenting, including the optimal stent length and type.[102,112]

SPECIAL CONSIDERATIONS IN MANAGEMENT

This section discusses some scenarios in which treatment strategies may vary from those for standard IIH, such as fulminant IIH and pregnancy.

Fulminant Idiopathic Intracranial Hypertension

Approximately 2% to 3% of patients with IIH present with a very severe form with rapid vision loss over days within 1 month of symptom onset, which is termed *fulminant IIH*.[113] Patients with fulminant IIH have severe papilledema, often grade 4 or 5, leading to progressive vision loss, presumably due to axoplasmic flow stasis and optic nerve ischemia.

Fulminant IIH is a neurologic emergency. Patients should be monitored very closely (often initially every day) and treated aggressively to try to prevent further vision loss and blindness. Patients should be immediately started on high-dose acetazolamide (often starting with 2000 mg/d and quickly escalating to 4000 mg/d), and temporizing IV methylprednisolone can be considered.[114] Most patients will require an urgent surgical intervention, which should be pursued immediately if the papilledema and vision loss are severe (CASE 5-2).

If surgery cannot be performed immediately, temporary CSF drainage, such as placement of a lumbar drain, should be strongly considered. In the largest case series of patients with fulminant IIH, just a short delay of a few days was associated with a significantly higher risk of blindness; those who did not become legally blind had a median time to surgical intervention of 2 days, whereas patients who became legally blind had a median time to surgical intervention of 6.5 days.[113] Surgical options include CSF diversion surgery, optic nerve sheath fenestration, and venous sinus stenting. Although there are several case series of treating fulminant IIH successfully with venous sinus stenting,[115] venous sinus stenting requires dual antiplatelet therapy after the procedure, which could potentially make subsequent additional surgeries more difficult if unsuccessful.

It is important to rule out mimics of fulminant IIH when patients present with bilateral optic disc edema and severe vision loss. With fulminant IIH, the papilledema should be very severe (at least grade 4) and fulfill the diagnostic criteria for IIH. If a patient has mild to moderate optic disc edema with profound vision loss, alternative etiologies should be sought, including neuroretinitis, papillitis, optic neuritis, and functional vision loss. Of particular importance, patients with myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) can present with bilateral optic disc edema that can be misdiagnosed as fulminant IIH. In addition, up to 21% of patients with MOGAD can have elevated opening pressure on lumbar puncture.[116] If the vision loss is out of proportion to the optic disc edema, MRI of the orbits with contrast is recommended to exclude bilateral optic neuritis, especially if the patient has eye pain.

Pregnancy

IIH is much more common in women of reproductive age than in men or other age groups.[6,117] One common misconception is that oral hormonal contraceptives cause secondary IIH. Case-control studies have shown that oral hormonal contraceptives do not appear to cause IIH and are not contraindicated in patients with IIH.[117] Weight gain associated with commencing hormonal contraceptives may be the reason for this misconception.[23] Appropriate counseling should occur when women of reproductive age start taking potentially teratogenic medications, especially topiramate. Acetazolamide has not been found to be teratogenic in humans, unlike topiramate; however, this observation is based on a small case series of 50 patients, and its continued use in the first trimester requires an individualized risk-benefit discussion.[118,119]

For the patient who becomes pregnant, regular monitoring of IIH activity reassures the patient and the obstetric team. A small amount of body weight gain is expected in pregnancy, but excessive weight gain has the potential to exacerbate IIH and increase maternal and fetal complications. A 2023

KEY POINTS

- **Papilledema almost always improves after venous sinus stenting, but 9% of patients require an additional surgical procedure, and severe adverse events occur in 2.3% of cases, which include thrombosis, stent migration, subdural or intradural hematoma, subarachnoid hemorrhage, and obstructive hydrocephalus.**

- **Most cases of fulminant IIH require urgent surgical intervention.**

- **Oral hormonal contraceptives are not contraindicated in patients with IIH and do not appear to cause IIH.**

- **Ideally, patients with IIH should aim to achieve disease remission or control before becoming pregnant, but IIH does not necessarily worsen during pregnancy if the patient gains the advised amount of weight during pregnancy.**

- **Polycystic ovarian syndrome can coexist with IIH.**

- **Antipsychotic medications can cause weight gain and may precipitate IIH.**

- **Headache in people with IIH mimics primary headache disorders, such as episodic migraine, chronic migraine, and tension-type headache.**

longitudinal cohort study found the IIH outcomes during pregnancy were favorable.[120] Patients with IIH are at increased risk of gestational diabetes, preeclampsia, and a complicated delivery, and hence, joint care with an obstetrician is important.[5] At delivery, if the papilledema is mild or moderate, a vaginal delivery may be deemed appropriate. In patients with severe papilledema, a prolonged second stage of labor is not recommended. Spinal and epidural anesthesia is not contraindicated, except in those few who have an

CASE 5-2

A 27-year-old woman was admitted emergently to the hospital. She had a 7-day history of worsening headache, blurred vision in both eyes, and transient visual obscurations. She reported occasional pulsatile tinnitus. On examination, her right visual acuity was 20/60, pinhole to 20/40, left visual acuity was 20/40 with no pinhole improvement. She had a mild left relative afferent pupillary defect. She had full-color vision in her right eye and 10/13 in her left eye on pseudoisochromatic plates. She had Frisén grade 4 papilledema in both eyes and significant elevation of the peripapillary retinal nerve fiber layer on optical coherence tomography imaging (FIGURE 5-8). Her visual fields showed severe bilateral generalized constriction. Her blood pressure was within normal range, and her BMI was 37 kg/m^2. Head CT and CT venogram were negative for a space-occupying lesion and cerebral venous sinus thrombosis. Her lumbar puncture opening pressure was 34 cm H_2O. Given the severe papilledema and significant vision loss, she was diagnosed with fulminant idiopathic intracranial hypertension.

Emergency same-day consultation with a neurosurgeon was made, and she underwent insertion of a ventriculoperitoneal shunt. Repeat eye examination (assessing for a reduction by one-third of the peripapillary retinal nerve fiber layer thickness on optical coherence tomography) before discharge 1 week after shunt placement showed adequate decompression of her papilledema. At 10 weeks, her papilledema was in total remission (FIGURE 5-8), but despite improvement, she had permanent visual field loss. With her permission, weight management was sensitively discussed. She was referred to the medical weight-management clinic and the sleep medicine and respiratory team for confirmation and treatment of obstructive sleep apnea.

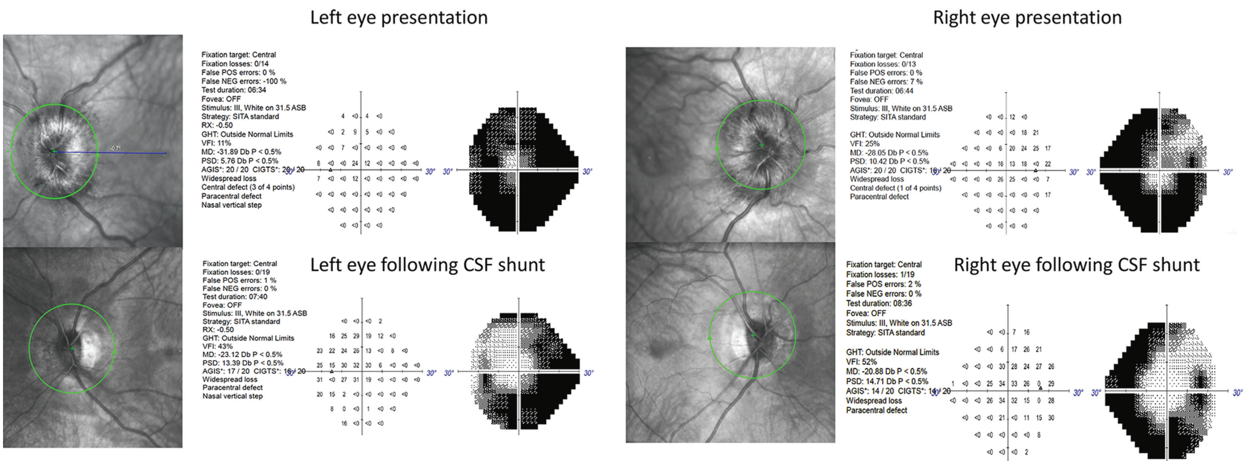
COMMENT

In this case, sight-threatening papilledema was indicated by reduced visual acuity, reduced color vision, a relative afferent pupillary defect, and visual field loss. Fulminant idiopathic intracranial hypertension requiring surgical intervention can occur at any time when the disease escalates, most commonly at initial presentation, but it can also occur with relapse of the disease. Typically, the lumbar puncture opening pressure is not a guide to the disease activity or when emergency management should occur, as evidenced in this case. The urgency of intervention is driven by the visual function and degree of papilledema. The type of surgical procedure depends on local expertise.

existing lumbar CSF shunt. After delivery, some patients may have weight gain, and therefore, it is useful to reexamine patients 3 to 4 months postpartum.

Polycystic Ovarian Syndrome

People with IIH have a 1.5-fold increased risk of comorbid polycystic ovarian syndrome,[8] which is phenotypically similar to IIH, being a hyperandrogenic disorder, but with a distinct hormonal profile.[121] The presence of polycystic



Left eye presentation

Fixation target: Central
Fixation losses: 0/14
False POS errors: 0 %
False NEG errors: -100 %
Test duration: 06:34
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: SITA standard
RX: -0.50
GHT: Outside Normal Limits
VFI: 11%
MD: -31.89 Db P < 0.5%
PSD: 5.76 Db P < 0.5%
AGIS*: 20 / 20 CIGTS*: 20 / 20
Widespread loss
Central defect (3 of 4 points)
Paracentral defect
Nasal vertical step

Right eye presentation

Fixation target: Central
Fixation losses: 0/13
False POS errors: 0 %
False NEG errors: 7 %
Test duration: 06:44
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: SITA standard

GHT: Outside Normal Limits
VFI: 25%
MD: -28.05 Db P < 0.5%
PSD: 10.42 Db P < 0.5%
AGIS*: 20 / 20 CIGTS*: 18 / 20
Widespread loss
Central defect (1 of 4 points)
Paracentral defect

Left eye following CSF shunt

Fixation target: Central
Fixation losses: 0/19
False POS errors: 1 %
False NEG errors: 0 %
Test duration: 07:40
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: SITA standard
RX: -0.50
GHT: Outside Normal Limits
VFI: 43%
MD: -23.12 Db P < 0.5%
PSD: 13.39 Db P < 0.5%
AGIS*: 17 / 20 CIGTS*: 16 / 20
Widespread loss
Paracentral defect
Nasal vertical step

Right eye following CSF shunt

Fixation target: Central
Fixation losses: 1/19
False POS errors: 2 %
False NEG errors: 0 %
Test duration: 08:36
Fovea: OFF
Stimulus: III, White on 31.5 ASB
Strategy: SITA standard

GHT: Outside Normal Limits
VFI: 52%
MD: -20.88 Db P < 0.5%
PSD: 14.71 Db P < 0.5%
AGIS*: 14 / 20 CIGTS*: 14 / 20
Widespread loss
Paracentral defect

FIGURE 5-8

Infrared optical coherence tomography visual field findings from the patient in CASE 5-2. *Top row*: Imaging at presentation shows grade 4 papilledema, and severely constricted visual fields are consistent with fulminant idiopathic intracranial hypertension. *Bottom row*: Imaging at 10 weeks after ventriculoperitoneal shunting shows resolution of the papilledema with some improvement in the visual fields but persistent arcuate visual field defects.

ovarian syndrome may influence weight management and fertility advice.[8,122] It does not appear to adversely affect visual or headache outcomes.[123]

Obstructive Sleep Apnea

There is some debate as to whether OSA is associated with IIH.[124] Uncertainty about this relationship is caused by different methods of diagnosing OSA, the definition of OSA, and the use of case-controlled studies rather than population-wide methodologies.[125] OSA is known to affect quality of life and increase the risk of cardiovascular disease, stroke, diabetes, hypertension, and hypercholesterolemia. OSA can contribute to early-morning headache and has the potential to contribute to worse visual outcomes.[126] It is, therefore, important to consider screening for OSA in patients with IIH, especially if they do not fit the typical demographic profile.[9]

Mental Health

Mental health disorders, depression, and anxiety frequently can coexist with IIH and may confer worse outcomes.[10,127,128] It is incompletely understood what drives poor mental health, which may be at least in part a result of living with obesity and chronic headache.[10] Because some antipsychotic drugs can precipitate weight gain, a temporal relationship between weight gain and a causative medicine should prompt the clinical team to discuss alternative options with patients and their mental health teams. There was a concerning finding in the Intracranial Hypertension Registry cohort: The risk of suicide was more than 6 times greater and the risk of death from accidental overdose was more than 3 times greater in patients with IIH compared with the general population. Furthermore, the risk of suicide by presumed purposeful overdose was more than 15 times greater among this cohort than in the general population.[128]

TREATING HEADACHE IN PATIENTS WITH IDIOPATHIC INTRACRANIAL HYPERTENSION

Headache management remains a high priority because headache burden confers morbidity to most people with IIH.[3,10] The headache tends to be moderate to severe in the setting of IIH. Headache attributed to increased ICP mostly lacks distinctive features, with a phenotype most often similar to that of primary headache disorders such as episodic migraine and tension-type headache.[129] A potential differentiator is that headaches associated with increased ICP are often present and sometimes the worst on awakening, which is not commonly seen in other primary headache disorders. Early in the disease, it is appropriate to focus on reducing the ICP and consider simple analgesia, such as acetaminophen or nonsteroidal anti-inflammatory drugs, because the headache symptoms can settle with treating the ICP.[13,14] Counseling regarding excessive analgesic use can help avoid medication-overuse headache. Opioids or ergots should not be used to treat IIH-related headache.

Once the ICP has normalized and the papilledema is resolving, it is an opportune time to repeat the characterization of the headache and reconsider treatment (CASE 5-3).

More than half of patients with IIH will have persistent headaches even after normalization of the ICP; for more information, refer to the article "Treatment of Persistent Headache After Normalization of CSF Pressure" by Olga Fermo, MD,[130] in this issue of *Continuum*. Treating the headache may abolish the

CASE 5-3

A 22-year-old woman was diagnosed with idiopathic intracranial hypertension 3 years ago. Her papilledema resolved after treatment with weight loss and acetazolamide. Her medical history included treatment for migraine, depression, and fibromyalgia. At a follow-up visit to neuro-ophthalmology clinic, she reported 28 monthly headache days and 20 migraine-like headache days per month with no headache-free days experienced since she was diagnosed with idiopathic intracranial hypertension. She also reported "brain fog" with difficulty concentrating and processing information. She took daily codeine for the headache with no effect. She tried headache medicines at clinically relevant doses, including pizotifen (a tricyclic agent she took as an adolescent for migraine), amitriptyline, nortriptyline, and candesartan.

On examination, her visual acuity was 20/20 uncorrected in both eyes, and she had normal color vision and no papilledema. She had persistently unreliable visual fields. Optical coherence tomography, including peripapillary retinal nerve fiber layer and ganglion cell layer thicknesses, was normal. Her BMI was 32 kg/m^2. Her Headache Impact Test (HIT-6) score was 73, and on the Hospital Anxiety and Depression Scale (HADS), her hospital anxiety score was 11 (moderate) and her depression score was 10 (mild).

She was counseled regarding medication-overuse headache and advised to discontinue codeine-based medicines. Triptan "triple therapy" was recommended, which entailed a triptan medicine taken with simple analgesia (such as nonsteroidal anti-inflammatory medicines or acetaminophen) and an antiemetic (usually a dopamine-receptor antagonist), which in this case reduced the severity and disability of the migraine-like attacks. Topiramate was considered, but given her history of depression and high hospital depression score, this was avoided. She was referred for subspecialty headache consultation. A calcitonin gene-related peptide antagonist was started. At her 6-month headache follow-up, she reported a 40% reduction in monthly migraine days.

COMMENT

The risk of medication-overuse headache must always be addressed because it can worsen headache morbidity and complicate headache management. Many patients will have persistent chronic migraine-like or tension-type headaches despite treatment of increased intracranial pressure, and, as in this case, prophylactic treatment should be considered. Each therapeutic trial of preventative medication should be started slowly and increased to an appropriate therapeutically tolerated dose for at least 3 months.

warning symptoms of IIH progression and, if unobserved, could lead to a relapse of papilledema, risking visual function. Hence, all patients should be counseled about weight gain throughout follow-up and the potential for relapse.[131]

CONCLUSION

Monitoring and treating people with IIH require a combination of skills in assessing visual function and headache symptoms. People with IIH are best monitored by both a neurologist and an ophthalmologist. The principles of management must address the rapidity of the disease that may lead to visual loss in some patients and necessitate emergency intervention and, in the longer term, the morbidity of headache that substantially affects the quality of life in most patients with IIH. Modifying the underlying risk factor of recent weight gain or obesity may require collaboration with an endocrinologist or weight-management specialist.

VIDEO LEGENDS

VIDEO 5-1
Cross-sectional video of a normal optic nerve. Optic nerve head protocol on optical coherence tomography is used to image a normal right eye. As the video scrolls through the nerve, the dip of the optic disc cup is visible.

VIDEO 5-2
Cross-sectional video of an optic nerve with moderate papilledema. Optic nerve head protocol on optical coherence tomography shows left optic disc swelling from increased intracranial pressure, which is moderate but not vision-threatening. There is also evidence of a peripapillary hyperreflective ovoid mass structure that encircles the optic nerve like a *C*-shaped donut and elevates the retinal layers further.

VIDEO 5-3
Cross-sectional video of an optic nerve with severe vision-threatening papilledema. Optic nerve head protocol on optical coherence tomography shows clear evidence of papilledema, which becomes more sight-threatening with early fluid underneath the optic nerve head on the temporal side of the nerve in the middle of the video and evidence of intraretinal fluid (black circular changes in the retinal layers).

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Atraumatic Cranial CSF Leaks

By Erin K. O'Brien, MD; Maria Peris Celda, MD, PhD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: This article reviews the most common presenting symptoms and radiographic findings of atraumatic cranial CSF leaks, surgical management of skull base leaks, and postoperative management of idiopathic intracranial hypertension (IIH).

LATEST DEVELOPMENTS: IIH is now widely accepted as a causative factor in the development of thinning of the bone of the anterior and lateral skull base and formation of encephaloceles or arachnoid granulations through the skull base with resulting CSF leaks into the aerated sinuses or middle ear and mastoid cavities. Demographic characteristics and presenting symptoms may differ slightly between patients with IIH and those with CSF leaks, but in both populations, management of elevated intracranial CSF pressure is required. Dural venous stenosis is associated with both conditions, and stenting of transverse or sigmoid sinus stenotic segments is now considered a treatment option for IIH.

ESSENTIAL POINTS: Atraumatic cranial CSF leaks present with clear fluid either dripping from the nose or accumulating in the middle ear and mastoid because of bony and dural defects in the anterior or lateral skull base. Cranial CSF leaks are often associated with IIH, and treatment requires both repair of the skull base defects and management of IIH. Timely diagnosis and treatment of CSF leaks and IIH are necessary to prevent meningitis and decrease the risk of recurrence of leaks or sequelae of IIH. Patients with these CSF leaks should be evaluated for IIH by imaging or postoperative lumbar puncture with opening pressure because pressure may increase further once the CSF leak is repaired. Medication, weight loss, and CSF shunting are management options for elevated CSF pressure, but imaging for intracranial venous stenosis should be considered with venous stenting for treatment of elevated venous pressure.

INTRODUCTION

Cranial CSF leaks occur through bony and dural defects in the anterior skull base into the aerated paranasal sinuses or through defects in the lateral skull base through the tegmen of the temporal bone into the aerated mastoid or middle ear spaces. Cranial CSF leaks can develop after head trauma, skull base surgery, or radiation or may occur spontaneously without a history of trauma. Atraumatic CSF leaks, typically unilateral, cause nasal dripping or middle ear fluid accumulation. Although these

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atraumatic leaks are commonly referred to as *spontaneous* leaks, increasing evidence shows that anterior or lateral skull base CSF leaks, the latter having an estimated incidence of up to 2.5 cases per 1 million people per year,[1] are sequelae of elevated intracranial pressure. This article discusses the clinical presentation, imaging, laboratory confirmatory testing, and surgical and postoperative management of skull base CSF leaks and idiopathic intracranial hypertension (IIH).

PRESENTATION

A CSF leak from the anterior or lateral skull base presents as unilateral clear fluid dripping from the nose (CSF rhinorrhea), clear unilateral middle ear fluid or mastoid effusion, or clear fluid dripping from the ear in patients with a hole in the tympanic membrane from temporal bone defects (CSF otorrhea).

For patients with CSF rhinorrhea, the dripping from the nose is noted when leaning forward, and the fluid may have a salty taste.[2] Patients may also report a salty taste of fluid dripping into their throat. CSF rhinorrhea differs from rhinorrhea associated with allergic or nonallergic rhinitis in that CSF rhinorrhea is unilateral. Patients with CSF rhinorrhea may have been previously treated for allergic rhinitis or chronic sinusitis without improvement in their symptoms. In one study of patients with CSF rhinorrhea, 48% had been previously diagnosed with chronic sinusitis, although patients with a CSF leak typically reported primarily clear watery drainage and not the nasal obstruction or thick mucus associated with chronic sinusitis.[3] CSF rhinorrhea can also be differentiated from rhinitis by a trial of ipratropium topical nasal spray 0.06%; ipratropium can decrease mucus production associated with rhinitis, but CSF rhinorrhea will not improve with ipratropium spray.[4]

For CSF leaks in the temporal bone into the middle ear or mastoid, patients may have unilateral conductive hearing loss from fluid in the middle ear.[5] On examination, ear fluid may be seen behind the tympanic membrane on otoscopy. Patients may note nasal dripping or a salty taste in their throat from fluid draining from the middle ear or mastoid through the eustachian tube into the nasopharynx and then into the nose or throat. If the patient has a myringotomy incision in the tympanic membrane or has had a tympanostomy tube inserted, clear fluid may drain from the middle ear, often soaking a pillow at night. Clinicians should be suspicious of a middle ear or mastoid CSF leak if a patient has a unilateral clear middle ear effusion.

IDIOPATHIC INTRACRANIAL HYPERTENSION AND CSF LEAKS

Spontaneous or idiopathic skull base CSF leaks are increasingly recognized as an associated symptom of IIH, as reviewed in the International Consensus Statement on spontaneous CSF rhinorrhea.[2] In 1994, there was a report of four patients with previous diagnoses of IIH who presented with spontaneous CSF rhinorrhea.[6] In 2003, 10 patients were reported to undergo successful surgical repair of CSF rhinorrhea; these patients postoperatively developed headaches, pulsatile tinnitus, or balance problems and opted to have lumbar puncture for pressure measurement, on average 14 months after surgery.[7] All 10 patients had elevated intracranial pressure on the postoperative lumbar puncture and had preoperative imaging showing an empty or partially empty sella. The authors concluded that CSF rhinorrhea is likely associated with intracranial hypertension, requiring postoperative assessment of intracranial pressure and appropriate management.

Patients who present with spontaneous skull base CSF leaks and patients without a leak who have intracranial hypertension have similar demographic characteristics except for age. Patients with skull base CSF leaks, as described in a 2017 systematic review, are frequently obese (80%) with body mass indices (BMIs) in the range of 35 to 38 kg/m^2, are more likely to be female (77% for anterior skull base and 65% for lateral skull base leaks), have an increased likelihood of a diagnosis of obstructive sleep apnea (43%), and are, on average, 57 to 60 years old.[8,9] Patients with IIH without CSF leaks also tend to be female and have an elevated BMI, although the age at presentation is younger (36 years old) than patients with CSF leaks.[10]

Patients with spontaneous skull base CSF leaks may have symptoms commonly associated with IIH, although overall, these other symptoms are less frequent than are reported in patients with IIH. A 2019 review of IIH and CSF leaks summarized the incidence of IIH symptoms in both groups, with headache in 60% of the patients with CSF leaks and 90% of the patients with IIH, pulsatile tinnitus in 20% of patients with CSF leaks and 60% of patients with IIH, and diplopia in 5% of patients with CSF leaks and 30% of patients with IIH.[10] Papilledema, however, is one of the major criteria for diagnosis of IIH, but it is rarely seen in patients with spontaneous skull base CSF leaks, presumably because intracranial pressure is being relieved by the active leakage of CSF.[10-12]

Patients with skull base CSF leaks may present with meningitis. The percentage of patients with a history of meningitis and spontaneous CSF leaks is estimated at approximately 10% (higher in patients with traumatic CSF skull base leaks).[13-16] The most common bacteria associated with meningitis in patients with CSF leaks is *Streptococcus pneumoniae*, although unencapsulated *Haemophilus influenzae* has also been reported.[15] In addition to the risk of meningitis, patients with spontaneous CSF leaks may also present with aspiration pneumonitis in those who have impaired swallowing reflexes or need long bed rest.[17]

IMAGING

Cranial imaging to investigate spontaneous CSF leaks includes primarily CT and MRI.

The main characteristics that can be identified from noncontrast high-resolution CT of the sinuses and anterior skull base or temporal bone include bony defects, especially in the anterior skull base facing the sinuses or floor of the middle fossa at the tegmen tympani or tegmen mastoideum.[18,19] Indirect signs such as opacification of the sinuses or mastoid and middle ear are nonspecific but can point toward the area of dehiscence.[20] The accuracy of CSF leak localization with high-resolution CT is 87% to 98% with high positive predictive values.[21]

The most common locations for anterior skull base spontaneous CSF leaks into the sinuses are the cribriform or ethmoid roof (**FIGURE 6-1**) or the lateral recess of the sphenoid sinus (**FIGURE 6-2**).[16,20] Patients with skull base CSF leaks frequently have multiple sites of osseous defects in the skull base and arachnoid pits.[22] CSF leaks occur at sites of thin bone of the skull base adjacent to pneumatization, either at the cribriform, which is penetrated by ostia for olfactory fila, or in the lateral recess of the sphenoid, lateral to foramen rotundum.[20,23,24] Patients with CSF leaks into the sphenoid bone are more likely to have pneumatized lateral sphenoid recesses than patients without CSF leaks.[25] It is postulated that intracranial hypertension causes thinning of the skull base in some patients, causing CSF leaks through the cribriform, thin ethmoid bone, or

KEY POINTS

- ● Anterior or lateral skull base CSF leak should be considered in patients with unilateral clear dripping from the nose or unilateral clear fluid in the middle ear.
- ● Treatment of patients with clear rhinorrhea with a trial of ipratropium nasal spray can differentiate rhinitis, which improves with ipratropium, versus CSF rhinorrhea, which does not improve with ipratropium.
- ● After surgical repair of an anterior or lateral skull base CSF leak, patients may present with symptoms of intracranial hypertension and elevated CSF pressure.
- ● Skull base CSF leaks are associated with intracranial hypertension, although typically without a clinical history of papilledema, and these patients are at risk of meningitis.
- ● Thin-cut noncontrast CT scans of the sinuses or temporal bone can identify bony defects through the ethmoid, cribriform, or lateral sphenoid sinus or through the tegmen mastoideum or tegmen tympani of the temporal bone with opacification of the sinuses, mastoid, or middle ear, respectively.
- ● Imaging may identify an encephalocele along the cribriform or in the lateral sphenoid along with fluid in the sinus for anterior skull base leaks or an encephalocele through the tegmen tympani with fluid in the mastoid and middle ear in lateral skull base leaks.

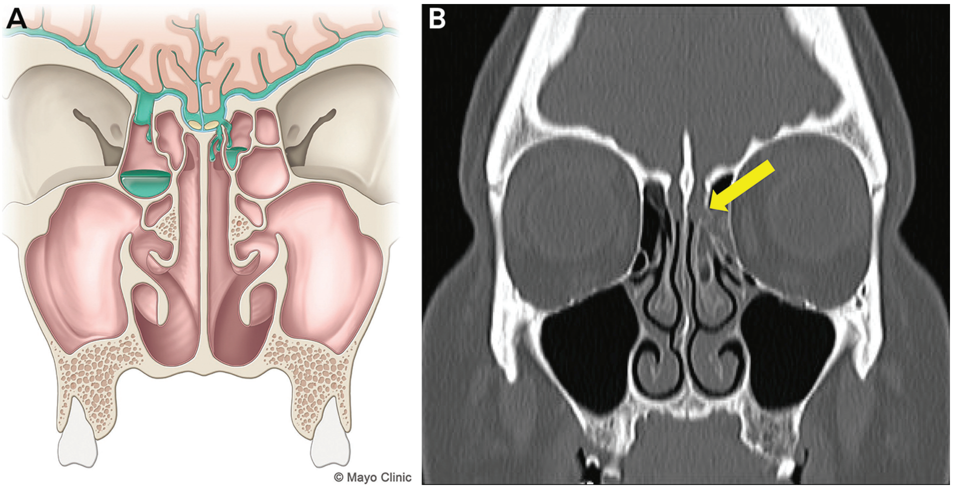

FIGURE 6-1

Anterior skull base ethmoid and cribriform CSF leak. *A*, Anterior skull base CSF leaks (represented here as *green fluid*) can occur at the roof of the ethmoid sinus (*left side*) or through the cribriform medially into the nasal cavity or at the lateral lamella of the cribriform into the anterior ethmoid sinus (*right side*). *B*, Coronal CT shows a lateral cribriform CSF leak with bony defect (*arrow*) and fluid opacification in the anterior ethmoid sinus.

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lateral sphenoid sinus in some patients, whereas in patients with IIH with thicker bone, there is no development of a CSF leak but rather other sequelae of IIH such as papilledema and headaches.[10]

Lateral skull defects with CSF leaks into the mastoid or middle ear occur at the tegmen mastoideum region of the temporal bone, a thin area of bone that faces the mastoid, or through the tegmen tympani into the middle ear (FIGURE 6-3).[19] The fluid permeates through the mastoid air cells or middle ear, accumulates in

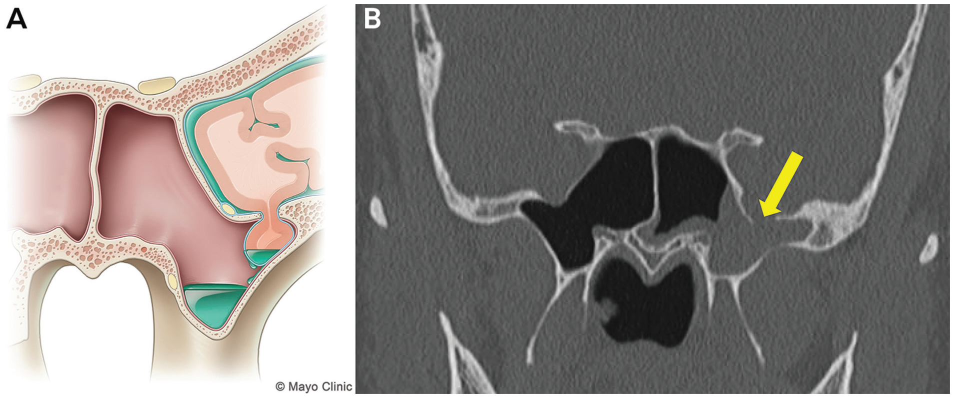

FIGURE 6-2

Lateral sphenoid CSF leak. Anterior skull base CSF leaks can occur into the sphenoid sinus lateral to V2 into a pneumatized lateral sphenoid space. *A*, A meningoencephalocele extends through a bony defect in the lateral sphenoid sinus with a leak of CSF (represented here as *green fluid*) into the sinus. *B*, Coronal CT shows a lateral sphenoid bony defect (*arrow*) with CSF and partial opacification of the sphenoid sinus.

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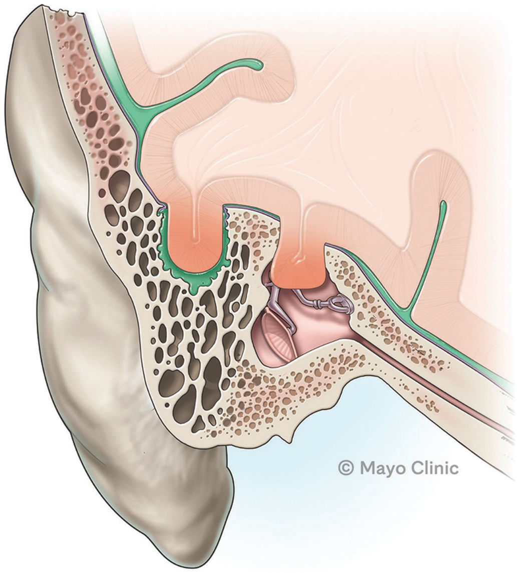

FIGURE 6-3

Lateral skull base temporal bone CSF leak through tegmen mastoideum and tegmen tympani. Lateral skull base CSF leaks can occur through the tegmen mastoideum into the mastoid, with meningoencephalocele extending through the bony defect or through the tegmen tympani into the middle ear.

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the tympanic cavity, and usually drains through the eustachian tube toward the nose and through a perforation in the eardrum, when present, toward the external acoustic canal. They are frequently associated with encephaloceles and, on many occasions, are bilateral.

In cases in which multiple bony defects are identified on high-resolution CT of the skull base, a CT cisternogram with intrathecal contrast may identify the site of an active CSF leak. Delayed imaging in a prone position may identify extracranial contrast, extravasation of contrast into a meningocele or meningoencephalocele through the skull base, or contrast into a sinus or the mastoid or middle ear. CT cisternography has low sensitivity but high specificity in detecting the location of CSF leaks in the investigation of the location of the defect when it is not obvious on plain CT.[26]

MRI is essential to investigate the causes of increased intracranial pressure and secondary CSF leaks, such as intracranial tumors or pathologies that erode the cranial base. For instance, the medical treatment of large prolactinomas is a known cause of spontaneous CSF leaks.[27] MRI may also indicate the presence of meningoceles or encephaloceles, which indicate bony and dural defects and are highly specific in locating the CSF leak for repair. MRI can also identify additional findings associated with IIH, such as empty sella.[18]

Radionuclide imaging with intrathecal technetium-99 or indium-111 has been used in the past for the investigation of CSF leaks causing otorrhea or rhinorrhea. Detection of radioactivity on pledgets in the nose or wicks in the ear canal may confirm a CSF leak, but this test does not precisely identify the site of the leak and is not commonly used to confirm a CSF leak or in surgical planning.[26]

An MR venogram is useful in investigating stenosis of the venous sinuses, which can be treated with venous sinus stenting.[18] In a study comparing patients with spontaneous CSF leaks and patients with IIH without CSF leaks, the patients with leaks were more likely to have transverse venous sinus stenosis and arachnoid granulations projecting into dural venous sinuses than the patients with IIH alone.[28]

DIAGNOSIS OF CSF LEAKS

If possible, fluid should be collected from the nose or ear to confirm a CSF leak before surgical management. β-2 transferrin is a glycoprotein found in CSF,

KEY POINTS

- **CT cisternography with intrathecal contrast can be used to identify the source of active CSF leaks in patients with multiple skull base bony defects.**

- **MRI and MR venogram can identify meningoencephaloceles through skull base defects and findings associated with idiopathic intracranial hypertension, including empty sella and transverse sinus stenosis.**

- **Intrathecal radionuclide imaging is not useful for identification of the site of a skull base defect and is not commonly used for evaluation of a CSF leak.**

- **β-2 transferrin and β-trace protein are more sensitive and specific than glucose levels in the fluid or a ring or halo test for confirming CSF rhinorrhea or otorrhea.**

- **CSF leaks of the anterior or lateral skull base require surgical repair to decrease the risk of meningitis and to close the skull base defect.**

- **Endoscopic repair of anterior skull base CSF leaks in the ethmoid sinus, along the cribriform or in the lateral sphenoid sinus, with intradural and mucosal repair has a high rate of success and low rate of recurrence.**

- **Lateral skull base leaks require either a mastoidectomy or middle cranial fossa approach for surgical repair and, in some cases, a combination.**

perilymph, and vitreous and aqueous humor but not in nasal or ear secretions. Therefore, the detection of β-2 transferrin in fluid from the nose or ear is a highly reliable test for CSF, with a sensitivity of 97% and a specificity of 99% in patients with a high suspicion of CSF leaks.[29] β-2 transferrin is detected by electrophoresis or enzyme-linked immunosorbent assay (ELISA). Although β-2 transferrin can be detected for up to 14 days in CSF stored at room temperature, saliva or bacterial infection could degrade the protein, causing a false-negative result; storing the sample at 4°C (39°F) is recommended by most testing centers.[30] Intermittent leakage can make collecting fluid for testing difficult. The nasal or ear fluid can be collected on a small piece of cotton gauze, swab, or pledget (without adding other fluid) for testing for β-2 transferrin, although fluid amounts less than 0.5 mL may be less reliable.

An alternative to β-2 transferrin is β-trace protein. β-trace protein is found in CSF, nasal secretions, and serum, but CSF has significantly higher levels of β-trace protein than nasal secretions, with a cutoff value of 1.0 mg/L showing high specificity and sensitivity for diagnosis of CSF in nasal secretions.[31,32]

The glucose level in rhinorrhea or otorrhea is not an acceptable test for confirmation of CSF. Although CSF should have higher glucose levels than airway secretions, active mucosal inflammation or hyperglycemia can increase mucus glucose levels, leading to false positives.[21] The ring or halo test, in which nasal or middle ear fluid is blotted on white cotton sheets or towels to separate blood, mucus, and fluid, is also unreliable for assessing if secretions include CSF and should not be used for clinical decision-making regarding CSF leaks.[21]

MANAGEMENT

Skull base spontaneous CSF leaks require surgical management to decrease the risk of meningitis.[33] Preoperative oral acetazolamide therapy can decrease or stop CSF leaking, but surgical repair of the skull base defect with coverage of arachnoid granulations is still widely accepted as necessary to prevent meningitis and prevent recurrence of leaking.[34,35]

Surgical Treatment

Once the CSF leak has been diagnosed with a positive β-2 transferrin test result and ideally anatomically located with MRI or CT, surgery is indicated.

ANTERIOR SKULL BASE DEFECTS (FACING THE NASAL CAVITY OR PARANASAL SINUSES). Defects facing the nose and paranasal sinuses are usually repaired via an endoscopic endonasal approach (**CASE 6-1**). When the defect is not clearly visible in imaging, administration of intrathecal fluoresceine immediately before the surgical exploration can facilitate visualization because the CSF is intensely yellow-tinged. Intrathecal fluorescein positively identified the site of the CSF leak in 88.7% of cases in a systematic review, with a low complication rate from intrathecal fluorescein when used at lower doses (less than 50 mg, although the authors use 10 mg).[36,37] The most common defects involve the ethmoid, namely the cribriform plate and fovea ethmoidalis. The lateral recess of the sphenoid is another important source of CSF leaks and, to a lesser extent, the planum and other areas in the cranial base. Development of endoscopic techniques has facilitated the repair, and it is achieved with endonasal exposure of the defect with epidural exploration, coagulation of the encephaloceles when present, and intradural repair with biological material such as muscle, fascia, or fat graft or synthetic dural substitutes. This is usually followed by a mucosal repair, either a free mucosal graft or a nasoseptal flap, or another vascularized intranasal flap, with the flaps being used in cases of higher flow or larger defects. Endoscopic endonasal repair of anterior skull base CSF leaks has a high likelihood of success,

CASE 6-1

A 38-year-old woman was diagnosed with intracranial hypertension with headaches, unilateral facial paresthesia, and transient vision changes, which were worse with bending over. She had an elevated body mass index (BMI) greater than 40 kg/m^2, and an ophthalmic examination identified bilateral papilledema. MRI showed an expanded empty sella, prominent optic nerve sheaths, and mild posterior flattening of the globes. Lumbar puncture demonstrated an opening pressure of 26 cm H_2O, which decreased to 14 cm H_2O after removal of 30 mL of CSF, resulting in temporary improvement in her symptoms. Acetazolamide was stopped because of side effects; topiramate 100 mg 2 times per day resulted in some improvement in her symptoms. She declined a ventriculoperitoneal shunt for idiopathic intracranial hypertension.

Eight years later, she developed unilateral left clear nasal dripping. The nasal fluid was positive for β-2 transferrin, consistent with CSF rhinorrhea. CT of the sinuses revealed a defect in the lateral lamella of the cribriform plate of the ethmoid bone with fluid in the adjacent anterior ethmoid sinus.

CT venogram identified a high-grade stenosis of the right transverse and sigmoid sinus junction. After discussion with the patient and interventional neuroradiologist, neurologist, rhinologist, and neurosurgeon, the decision was made to perform stenting of the right transverse and sigmoid sinus stenosis before repair of the anterior skull base CSF leak. The prestenting pressure in the right superior sagittal sinus was 25 mm Hg (right jugular bulb, 15 mm Hg). After stenting of the transverse and sigmoid sinuses, the superior sagittal sinus pressure was 18 mm Hg. She was treated with antiplatelet therapy.

Three months after stenting, she underwent endoscopic repair of an anterior ethmoid cribriform CSF leak and encephalocele repair. A leaking encephalocele was identified in the ethmoid sinus at the cribriform. The dural defect was packed with a small piece of collagen-based dural graft material, and the bony defect was covered with a free mucosal graft and dissolvable dural sealant. She did well postoperatively with no further leaking of CSF during 2 years of follow-up after the procedure. Weight-loss treatment with phentermine decreased her BMI to 35 kg/m^2.

COMMENT

This case exemplifies the progression of idiopathic intracranial hypertension to an anterior skull base CSF leak with clear rhinorrhea. In this case, stenting of a stenotic portion of the sigmoid and transverse sinuses was performed before successful endoscopic repair of the anterior skull base encephalocele and CSF leak.

with reported rates of approximately 90%, and higher rates of recurrence of CSF leaks in patients with IIH.[8,38]

TEGMEN TYMPANI DEFECTS. The approach used to repair a tegmen tympani defect can be a middle fossa craniotomy, a mastoidectomy, or a combination of both (CASE 6-2). Surgery involves epidural exploration and coagulation of the encephaloceles when present and repair of the bony defect with an array of different techniques that can involve intradural and extradural repair, with or without rigid reconstruction with biological (temporalis fascia, pericranium, fat graft) and synthetic (dural substitutes, bone cement) materials. The goal of surgery is to recreate the barrier between the intracranial and extracranial space, and the technique depends on the surgeon's preference, the severity of the case, and the surgical anatomy of the patient. Both rigid and nonrigid repairs have comparable outcomes for complications or recurrent CSF leak rates, although rigid repair has been reported more frequently with larger defects (greater than 1 cm).[39]

CASE 6-2

A 55-year-old woman with a body mass index (BMI) of 60 kg/m^2 presented with ear fullness and decreased hearing in her left ear that started a few months before the visit. She was seen by an otolaryngologist and had an ear tube placed in her left ear. She had significant drainage after this procedure. This fluid was positive for β-2 transferrin. Lumbar puncture showed, despite ongoing aural drainage, a pressure of 25 cm H_2O. MRI (FIGURE 6-4) showed a left-sided encephalocele with fluid filling the mastoid, and CT showed a tegmen tympani defect. A CT venogram revealed stenosis of the right transverse and sigmoid sinus junction.

A middle fossa surgical approach was performed. The epidural exploration demonstrated dural defects and four encephaloceles, one of them with large dimensions, that were coagulated. The dura mater was repaired with an inlay collagen graft and temporalis fascia with an onlay temporalis muscle graft, pericranium, and temporalis fascia. The tegmen defect was repaired with bone cement as a rigid reconstruction. The patient recovered well from the operation with no further drainage, and she was discharged on postoperative day 2. Given the elevated pressure preoperatively, even with active drainage, the decision was made to offer her stenting of her right transverse and sigmoid sinuses to decrease the intracranial pressure. Three months after stenting and dual antiplatelet therapy, lumbar puncture demonstrated normalization of the intracranial pressure to 15 cm H_2O. The patient was counseled to start a weight-loss program and lifestyle modification to normalize her BMI and prevent further CSF leaks.

COMMENT

This case of clear otorrhea exemplifies a lateral skull base defect with a CSF leak associated with intracranial hypertension. Surgical repair plus transverse and sigmoid sinus stenting resulted in repair of the leak and reduction in intracranial pressure.

After surgery, a lumbar drain can be placed for a few days in certain cases, especially with high-flow leaks, to facilitate the healing process by reducing intradural pressure that can precipitate releaking.

Considerations for the Timing of the Repair

When a patient has an active leak, the pressure can be falsely lowered before the repair. In most cases, surgery for the repair is performed to reduce the long-term risk of meningitis. However, in cases in which the pressure is very high despite the CSF leak, reducing the intracranial pressure before the repair with medication, venous stenting, or CSF diversion could be an option to improve the chances of long-term surgical success of the repair.

Postoperative Management of Elevated Intracranial Pressure

Comorbid and underlying intracranial hypertension must be investigated and managed after CSF leak repair because elevated pressures can result in further

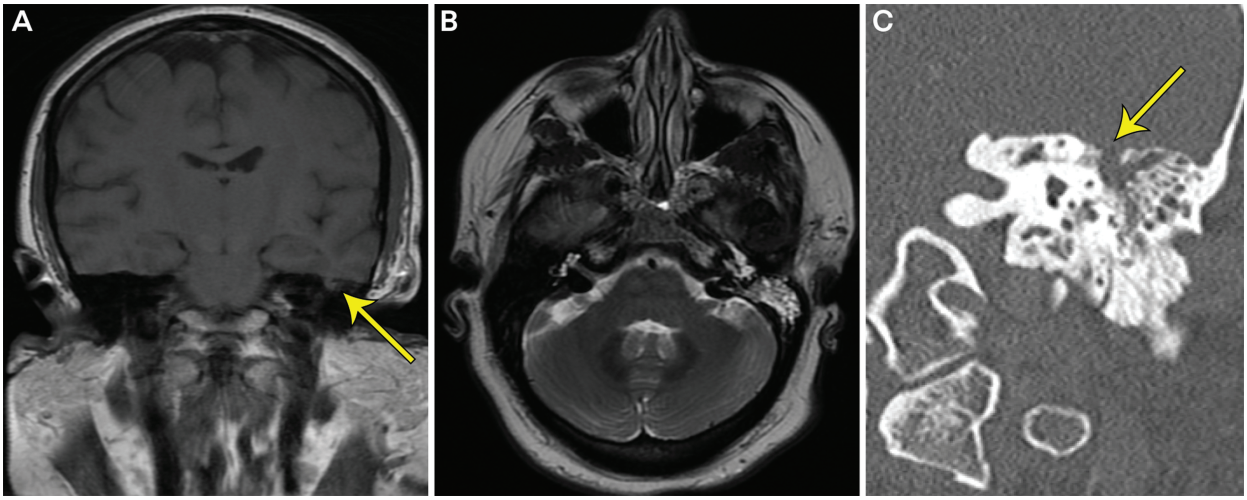

FIGURE 6-4
Lateral temporal bone CSF leak in the patient in CASE 6-2. *A*, Coronal T1-weighted MRI shows a left-sided encephalocele (*arrow*). *B*, Axial T2-weighted MRI shows fluid in the left mastoid. *C*, Temporal bone CT shows a tegmen defect (*arrow*).

symptoms and sequelae of IIH or recurrence of a CSF leak at the same or a different site in the skull base.[38] Lumbar puncture 24 hours to 1 month after surgical repair can provide an accurate measurement of opening pressure. Weight-loss programs, medical treatment (eg, acetazolamide, topiramate), and venous stenting in cases of venous sinus stenosis are essential to increasing the long-term success of the surgical repair and preventing ophthalmic complications and other spontaneous CSF leaks elsewhere in the cranial base. Pooled analysis of 679 patients treated for CSF rhinorrhea identified a higher success rate of surgical repair (ie, no recurrence of CSF leak) of 93% in patients actively treated for elevated intracranial pressure (with acetazolamide or lumboperitoneal or ventriculoperitoneal shunt) compared with the success rate of 82% for patients without active intracranial pressure management.[40]

Venous sinus stenosis has been increasingly recognized in spontaneous anterior skull base CSF leaks and IIH; several studies now demonstrate a reduction in intracranial pressures and improvement of symptoms of IIH with stenting of the stenoses in the transverse or sigmoid sinus.[41] Fewer data exist on the efficacy of stenting for the reduction of recurrence of CSF leaks after surgical repair, but one study demonstrated a lower rate of recurrent leaks after surgical repair and venous stenting in patients with venous stenosis compared with historical control patients who had repair before the option of stenting.[42] Additional studies are required to determine the long-term efficacy of venous stenting for the reduction of recurrence of CSF leaks, intracranial pressure, and sequelae of IIH in patients with CSF leaks.

KEY POINTS

- **Spontaneous skull base CSF leaks are frequently associated with intracranial hypertension, with worsening of elevated intracranial pressure after surgical closure of the leak site. In addition to surgical repair, management of intracranial hypertension is necessary to prevent the recurrence of leaks and potential sequelae of idiopathic intracranial hypertension.**
- **Active management of idiopathic intracranial hypertension along with surgical repair may include medical therapy such as acetazolamide, weight loss, CSF shunting, or stenting of venous sinus stenosis.**

CONCLUSION

Spontaneous anterior skull base CSF leaks are likely caused by intracranial hypertension, but these patients may present at an older age than those with IIH and are less likely to have papilledema as a presenting finding. Unilateral clear nasal or middle ear or mastoid fluid should be tested for β-2 transferrin to confirm a diagnosis of a CSF leak of the anterior or lateral skull base. CT of the skull base can confirm both the bony defect and CT venographic association with venous sinus stenosis. MRI and MR venography can identify encephaloceles at the leak site and radiographic findings associated with IIH (ie, empty sella and venous sinus stenosis). Surgical repair of the CSF leak is necessary to prevent meningitis. The long-term success of surgical repair improves with active management of postoperative intracranial hypertension. Management of IIH and postoperative CSF leak increasingly includes stenting of venous sinus stenosis.

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Treatment of Persistent Headache After Normalization of CSF Pressure

By Olga Fermo, MD

REVIEW ARTICLE

CONTINUUM AUDIO
INTERVIEW AVAILABLE
ONLINE

ABSTRACT

OBJECTIVE: **Headache is the most common symptom of intracranial hypertension and hypotension and may not remit after normalization of intracranial pressure. This article reviews the clinical presentation, mechanism, differential diagnosis, treatment, prognosis, and monitoring of persistent headache after normalization of intracranial pressure in the setting of idiopathic intracranial hypertension and spontaneous intracranial hypotension.**

LATEST DEVELOPMENTS: **Erenumab, a monoclonal antibody to the calcitonin gene–related peptide receptor, was shown to reduce headache frequency in the first-ever prospective study of headache treatment in patients with idiopathic intracranial hypertension in ocular remission. Similar avenues remain to be explored for spontaneous intracranial hypotension even though it has been shown that some patients continue with headache despite radiographic resolution of CSF leaks.**

ESSENTIAL POINTS: **Headache is the most common symptom to herald an intracranial pressure disturbance and may not resolve despite normalization of pressure. Neurologists must be aware that persistent headache does not automatically imply abnormal intracranial pressure in patients with previous disorders of CSF dynamics and informed of the possible alternative headache etiologies in these populations.**

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RELATIONSHIP DISCLOSURE:
Dr Fermo reports no disclosure.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Fermo discusses the unlabeled use of acetazolamide, topiramate, and venous sinus stenting for the treatment of idiopathic intracranial hypertension; amitriptyline, atogepant, candesartan, divalproex, eptinezumab, erenumab, fremanezumab, gabapentin, galcanezumab, memantine, onabotulinumtoxinA, pregabalin, propranolol, rimegepant, topiramate, venlafaxine, verapamil, and zonisamide for the treatment of migraine secondary to idiopathic intracranial hypertension (none of these are US Food and Drug Administration [FDA] approved for the treatment of idiopathic intracranial hypertension, but atogepant, divalproex, eptinezumab, erenumab, fremanezumab, galcanezumab,

Continued on page 789

INTRODUCTION

Despite disorders of intracranial pressure derangement causing myriad symptoms, headache is overwhelmingly the most common symptom of idiopathic intracranial hypertension (IIH)[1] and spontaneous intracranial hypotension (SIH).[2] IIH may first be recognized by an ophthalmologist, and patients with SIH may first present to a neuroradiologist or surgeon, but the patients who remain symptomatic are typically treated by neurologists. The chronic problem is often headache. Although some progress has been made in understanding persistent headache in patients with IIH, the same evidence has not been well explored for those with SIH.

IDIOPATHIC INTRACRANIAL HYPERTENSION

IIH is a condition of pathologically sustained intracranial hypertension culminating either in papilledema or bilateral sixth nerve palsy.[3] Although it is frequently associated with headache, sometimes as the first symptom,[1] for treatment purposes it is best to think about IIH as two separate conditions: an optic nerve disorder and a headache disorder.

Prevalence and Typical Headache Phenotype

Headache is the most common symptom of IIH, affecting 84% of the participants in the Idiopathic Intracranial Hypertension Treatment Trial, but even higher prevalence has been reported in other studies.[1] In describing their headaches, patients anecdotally say they feel head pressure, but more often than not the headache phenotype resembles migraine. When standardized criteria as published in the *International Classification of Headache Disorders, Third Edition*

TABLE 7-1

Diagnostic Criteria for Migraine Without Aura[a]

Description

- **Recurrent headache disorder manifesting in attacks lasting 4-72 hours; typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photophobia, and phonophobia**

Diagnostic criteria

A At least five attacks[b] fulfilling criteria B through D

B Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[c,d]

C Headache has at least two of the following four characteristics

  1 Unilateral location

  2 Pulsating quality

  3 Moderate or severe pain intensity

  4 Aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D During headache at least one of the following occurs

  1 Nausea or vomiting

  2 Photophobia and phonophobia

E Not better accounted for by another *International Classification of Headache Disorders, Third Edition*, diagnosis

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[a] Reprinted with permission from Olesen J, Cephalagia.[4] © 2013 International Headache Society.

[b] One or a few migraine attacks may be difficult to distinguish from symptomatic migraine-like attacks. Furthermore, the nature of a single or a few attacks may be difficult to understand. Therefore, at least five attacks are required. Individuals who otherwise meet criteria for 1.1 Migraine without aura but have had fewer than five attacks should be coded 1.5.1 Probable migraine without aura.

[c] When the patient falls asleep during migraine and wakes up without it, duration of the attack is reckoned until the time of awakening.

[d] In children and adolescents (younger than 18 years old), attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).

(TABLE 7-1[4]) were used to phenotype headache in the Idiopathic Intracranial Hypertension Treatment Trial, the most common patient experience was migraine (52%) followed by tension headache (22%) and probable migraine (16%), for a total of 68% of patients experiencing symptoms on the migraine spectrum.[1] In the same study, the prevalence of baseline migraine was approximately double what is normally seen in the general population,[1] whereas in a case-control study, patients were 6 times more likely to develop migraine headache than the general population.[5]

Response of Headache to Pressure Normalizing Treatment

Counterintuitively, the data indicate a pressure-independent mechanism of headache in most patients with IIH. This observation was demonstrated in many direct and indirect ways. A 12-month prospective study following the visual and headache outcomes of 35 patients with either diuretic-treated or shunt-treated IIH found that both papilledema and headache improved dramatically within the first month of treatment. For the rest of the year-long study, however, there was a divergence between the visual and headache outcomes. Although papilledema continued to improve for 12 months, improvement in headache plateaued at 1 month. At 12 months, 57% of patients continued to have headache despite ocular remission.[6] The Idiopathic Intracranial Hypertension Treatment Trial, the first blinded, randomized, controlled clinical trial studying the effect of acetazolamide on visual outcome, yielded insights on the lack of relationship between headache and pressure.[7] This study of 165 patients with papilledema and mild visual loss found no correlation between headache-related disability and stigmata of intracranial hypertension, including opening pressure, papilledema grade, and visual function at baseline.[7] Furthermore, the use of acetazolamide had no more impact than placebo on headache-related disability after 6 months of treatment, with close to 70% of all participants continuing to have headache.[1,7] Comparable results were seen for patients who underwent CSF diversion via ventricular or lumboperitoneal shunting, with separate studies showing continued rates of headache in 79% of patients at 24 months,[8] 42% at 35 months,[9] and 48% at 36 months.[10]

Akin to these studies, headache continues despite excellent ophthalmologic recovery after venous sinus stenting is performed. A retrospective review of 86 patients, nearly all of whom had headache at baseline, found that 83.5% of patients with IIH continued to have headache 3 months after venous sinus stenting despite significant improvement in papilledema grade and peripapillary retinal nerve fiber layer thickness, although in about 73% of the patients the headache was classified as improved.[11] It is difficult to judge the effect of venous sinus stenting on long-term headache control from the current landscape of studies for many reasons, including variable durations of follow-up and nonspecific outcome measures (eg, headache improvement rather than improvement in headache frequency or headache-related disability). For example, a 2024 meta-analysis included 24 articles with clinical follow-up ranging from 7 to 35.5 months where available, finding 73% of patients with improvement in headache after venous sinus stenting but overall 95% of patients with persistent headache.[12]

Pressure-independent Headache

Central sensitization is the likely mechanism of pressure-independent headache in patients with IIH.[13] Much of the understanding of intracranial nociception

KEY POINTS

- **Headache is the most common and often first symptom of idiopathic intracranial hypertension (IIH). The phenotype most often resembles migraine.**
- **Patients with IIH are 6 times more likely than the general population to develop migraine.**
- **Most patients with IIH continue to have headaches after remission of papilledema.**
- **Pressure-lowering treatments (ie, acetazolamide, stenting, shunting) typically do not improve headache symptoms after pressure has normalized.**

originated from observations during neurosurgeries on patients who were awake and finding the meninges, meningeal vessels, dural sinuses, proximal arteries of the circle of Willis and possibly smaller cerebral vessels, and the pia mater as pain-sensitive structures.[14] These structures are innervated by the first division of the trigeminal nerve supratentorially and by the upper cervical spinal nerve roots and sensory fibers of the facial, glossopharyngeal, vagus, and hypoglossal nerves infratentorially.[14] The connections formed between cranial blood vessels, the trigeminal and posterior fossa nociceptors, and their convergence at the level of the trigeminal nucleus caudalis in the brainstem and upper cervical spinal cord are called the *trigeminovascular system*, which is the final common pathway for manifesting primary and secondary head pain.[14]

Sensitization occurs when the trigeminovascular system develops amplified responses to painful or nonpainful stimuli. Central sensitization implies transmission is enhanced at the level of the second-order nociceptive neuron in the brainstem, initiating stimulus-independent activity.[15] The clinical marker of central sensitization is cutaneous allodynia,[15] when the scalp is tender outside the original area of pain and nonpainful stimulation, such that combing hair or wearing eyeglasses is perceived as painful.[16] A study of 46 patients with IIH found that one-half experienced cutaneous allodynia, implying that central sensitization had occurred.[16]

The exact trigger for migraine pain in the setting of IIH remains to be confirmed.[17] One postulated mechanism of trigeminovascular system activation (required for development of central sensitization) involves the cerebral venous circulation. The human superior sagittal sinus and cortical bridging veins were found to contain large amounts of calcitonin gene–related peptide, an obligatory neuropeptide to the migraine pathway.[18] De Simone and colleagues[18] hypothesized that the dural venous sinus congestion (upstream of venous sinus stenosis) encountered in patients with IIH could lead to a continuous activation of calcitonin gene–related peptide, thereby sensitizing the central migraine processing pathways.

Another postulated mechanism is the development of meningeal hypersensitivity to mechanical stimulation. Animal studies performed by Strassman and colleagues[19] showed that chemical sensitization of dural nociceptors caused enhanced responses to subsequent mechanical stimulation and even new responses in some neurons that were not previously mechanosensitive. That work intended to elucidate how patients with migraine develop meningismus-type symptoms and introduced the idea that chemically sensitized meningeal nociceptors could become mechanosensitized through normal fluctuations in intracranial pressure, such as those accompanying the normal vascular pulsation cycle, bending over, or performing Valsalva maneuvers.[15,19]

Although similar work has not been performed in the setting of IIH, taking these ideas together could explain initial pressure-dependent head pain followed by pressure-independent head pain. According to the work of De Simone and colleagues,[18] the changes occurring at the level of the venous sinuses stimulate chemical sensitization through activation of the calcitonin gene–related peptide pathway,[18] which could in turn provide the necessary nidus for hypersensitivity to even routine intracranial pressure escalations according to the work of Strassman and colleagues.[19] Theoretically, there could come a point when the meningeal nociceptors are so chemically and mechanically sensitized that sustained intracranial hypertension is no longer required for stimulation,[17] potentially explaining the persistence of headache after ocular remission,[6] continued headache-related disability despite acetazolamide treatment,[7] and lack of long-term headache response after shunting.[8-10]

Differential Diagnosis of Persistent Headache

Potential etiologies of persistent headache despite ocular remission in any patient with IIH include pressure-independent headache (typically migraine), medication-overuse headache, obstructive sleep apnea, postdural puncture headache, and spontaneous spinal CSF leak. Causes of persistent headache despite ocular remission in patients with IIH treated surgically include ventricular or lumbar shunt overdrainage, postcraniotomy headache, venous sinus stent-related headache (stent thrombosis or oversized stent), and "shuntalgia" (shunt-related scalp allodynia).

Although the evidence supports that most patients with IIH will continue to have migraine-like headache after achieving ocular remission, it is important to consider other etiologies of secondary headache, particularly the disorders these patients are uniquely prone to. In this author's experience, migraine-like headaches respond quickly and well to evidence-based chronic migraine treatment strategies. If patients do not respond to headache treatment as expected, the diagnostic possibilities should be revisited. This includes performing repeat optic nerve assessments and radiographic studies as appropriate to evaluate for recurrent intracranial hypertension, screening for a sleep-related breathing disorder, and considering the possibility of postdural puncture headache[20] even in the chronic setting,[21] or spontaneous spinal CSF leak.[22]

Treatment

To date, no randomized controlled trials have confirmed the efficacy of any headache-focused treatment in the setting of IIH.[3] Expert consensus guidelines published in 2018 advised treating long-term headaches according to the phenotype, which, as stated earlier, is most often migrainous.[3] The migrainous phenotype includes headaches that are moderate to severe in intensity, may be throbbing, are worsened by routine physical or mental exertion, and are associated with photophobia, phonophobia, nausea, or vomiting.[4] Headaches that are milder in intensity, lack the throbbing quality, are mild to moderate in intensity, are not aggravated by routine activity, are not associated with nausea or vomiting, and have no more than either photophobia or photophobia are defined as a tension phenotype.[4]

WHEN TO OFFER HEADACHE TREATMENT. Large, longitudinal population studies on migraine found several risk factors for the progression of infrequent migraine to chronic migraine, defined as having 15 or more headache days per month. These risk factors were stratified as nonmodifiable or not easily modifiable (age, sex, history of head injury, socioeconomic status) versus modifiable (headache frequency, presence of allodynia, obesity, analgesic medicine overuse, depression, stressful life events, caffeine overconsumption, and snoring).[23] These modifiable risk factors became important targets, with preventive treatment to reduce headache frequency being a cornerstone. A mean monthly headache frequency of 5 to 9 days per month increased the odds of developing chronic headache about 6-fold, whereas a mean monthly headache frequency of

KEY POINTS

- The trigeminovascular system is the final common pathway for manifesting both primary and secondary head pain.
- A wide array of headache mechanisms should be considered in patients with IIH who continue to experience headache, including a sleep-related breathing disorder, iatrogenic intracranial hypotension, or spontaneous intracranial hypotension (SIH).
- There are no randomized trials to guide appropriate headache treatment in patients with IIH. Expert consensus recommends matching treatment to headache characteristics, following the guidelines for primary headache disorders.

TABLE 7-2 Preventive Treatments for Chronic Migraine Secondary to Idiopathic Intracranial Hypertension[a]

Medication	Dosing	Interaction with diuretics	Weight neutral	Reproductive considerations
High-efficacy treatments suitable for use in idiopathic intracranial hypertension (IIH)				
Topiramate	25-200 mg/d orally	Yes (avoid mixing diuretics)	Weight loss possible	Teratogenic; stop when planning conception and pregnancy
OnabotulinumtoxinA	155 units subcutaneously (SC) every 12 weeks[b]	No	Yes	Use in pregnancy not currently recommended; postmarketing real-world evidence failed to show any safety concerns in pregnant women exposed to ontabotulinumtoxinA
Erenumab	70 mg SC monthly	No	Yes	Stop 5 months before conception; recommended to avoid if patient desires near-term pregnancy or is not using reliable contraception
Fremanezumab	225 mg SC monthly or 675 mg SC every 3 months	No	Yes	Stop 5 months before conception; recommend to avoid if patient desires near-term pregnancy or is not using reliable contraception
Galcanezumab	240 mg SC initial loading dose followed by 120 mg SC monthly	No	Yes	Stop 5 months before conception; recommended to avoid if patient desires near-term pregnancy or is not using reliable contraception
Eptinezumab	100, 200, or 300 mg IV every 3 months	No	Yes	Stop 5 months before conception; recommended to avoid if patient desires near-term pregnancy or is not using reliable contraception
Rimegepant	75 mg orally disintegrating tablet every other day[c]	No	Yes	Stop when planning conception and pregnancy
Atogepant	60 mg orally daily[d]	No	Yes	Stop when planning conception and pregnancy
High-efficacy and probable-efficacy treatments to use with caution in IIH				
Propranolol	120-240 mg orally daily	No	Caution	Preferred treatment of headache in pregnancy if required
Amitriptyline	10-200 mg orally daily	No	No	Second-line choice in pregnancy if required

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Medication	Dosing	Interaction with diuretics	Weight neutral	Reproductive considerations
Probable-efficacy treatments suitable for use in IIH				
Venlafaxine extended release	150 mg orally daily	No	Yes	Preferred drug except during pregnancy; stop when planning conception and pregnancy
Miscellaneous treatments with variable efficacy but adequate safety profile in IIH				
Candesartan	16 mg orally daily	No	Yes	Teratogenic; stop when planning conception and pregnancy
Memantine	5-20 mg orally daily	No	Yes	Second line in pregnancy if required
Duloxetine	60-120 mg orally daily	No	Caution	Stop when planning conception and pregnancy
Zonisamide	100-400 mg orally daily	No	Yes	Stop when planning conception and pregnancy
Treatments to avoid in IIH				
Divalproex and sodium valproate	400-1000 mg orally daily	Yes[e]	No	Teratogenic; stop when planning conception and pregnancy
Gabapentin	Up to 2400 mg orally daily	No	No	Possibly safe based on limited data
Pregabalin (low efficacy)	50 mg orally 2 times a day	No	No	Only limited data available; possibly teratogenic
Verapamil (low efficacy)	120-480 mg orally daily	No	Yes	Possibly safe in pregnancy

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[a] Data adapted from the 2012 American Headache Society/American Academy of Neurology Guidelines for Prevention of Episodic Migraine,[28] available evidence,[29-32] and the opinion of this author combining efficacy in clinical practice and suitability to the side effect profile desired in IIH management and not based on direct comparisons among therapies in clinical trials.

[b] Provider-administered treatment.

[c] Avoid concomitant administration with strong inhibitors of CYP3A4; strong or moderate inducers of CYP3A.

[d] Avoid concomitant administration with strong inhibitors of CYP3A4; strong or moderate inducers of CYP3A4; reduce dose to 30 mg daily for OATP inhibitors.

[e] Concurrent use of divalproex or sodium valproate and topiramate may result in an increased risk of hyperammonemia, encephalopathy, and hypothermia.

10 or more increased the odds of developing chronic headache 20-fold.[24] Based on these results, experts recommend that prevention should be offered to patients with migraine depending on the monthly headache frequency and level of impairment caused by headache. Prevention should be offered or considered for those who experience fewer than 6 headaches per month with associated impairment or need for bed rest and offered to any patient who experiences 6 or more headache days per month regardless of the level of impairment.[25] Similar work in a large cohort of patients with IIH found a worse long-term headache prognosis when baseline headache frequency was already daily.[26]

TREATMENT OPTIONS. Like primary migraine, much of the treatment of migraine associated with IIH is unlabeled,[3] and drug choice depends on relative efficacy, tolerability, drug-drug interactions, and expected side effect profiles.[27] For IIH specifically, considerations include interaction with concurrent diuretic treatment (for papilledema), expected effect on weight and the efficacy of contraceptives, and the safety profile of the drug in pregnancy (because IIH disproportionally affects girls and women of reproductive age).[3] Individual choices are discussed in the following paragraphs and presented in **TABLE 7-2**.[28-32]

To date, one prospective open-label study has evaluated the efficacy of a headache preventive in patients with IIH. Fifty-five patients with chronic headache and IIH in ocular remission received erenumab, a monthly injectable monoclonal antibody to the calcitonin gene–related peptide receptor, for 12 months. At 12 months, erenumab reduced the frequency of monthly moderate to severe headache days by 11 and any-severity headache days by 13.[17] The study also showed that erenumab was similarly effective in patients who had no previous history of migraine before developing IIH and, separately, that it retained efficacy in those who met criteria for medication-overuse headache. The authors postulated that this improvement further supported the mechanistic role of calcitonin gene–related peptide in generating headache associated with IIH, especially when considering these were patients with long-duration, medically refractory chronic headache.[17]

Four other commercially available treatments are targeted to antagonizing calcitonin gene–related peptide, including the quarterly IV infusion of eptinezumab, monthly or quarterly subcutaneous injection of fremanezumab, monthly subcutaneous injection of galcanezumab, daily oral atogepant, and every-other-day oral rimegepant.[33,34] None of these other calcitonin gene–related peptide ligand or receptor antagonists have been studied in the treatment of migraine-like headache in the setting of IIH, yet they are attractive options because of their easier adherence, tolerability, high efficacy, lack of interaction with diuretics, and weight-neutral status. Furthermore, the injectable formulations bypass concerns regarding gastrointestinal absorption in patients with IIH who have undergone bariatric surgery. These agents are not recommended for use in pregnancy, due to evidence of placental transfer and unknown fetal effects of calcitonin gene–receptor peptide blockade.[33] When choosing this class, one should be mindful of patients' pregnancy plans and contraceptive methods, because the monoclonal antibody injections have a long half-life and ideally should be stopped 5 months before conception. If a female patient has near-term conception plans or is not actively preventing pregnancy, oral calcitonin gene–related peptide antagonists should be considered over monoclonal antibodies because of their shorter half-lives.

Botulinum toxin has well-established efficacy in the prevention of chronic migraine.[35] Although randomized, placebo-controlled trials of botulinum toxin have never been performed for patients with IIH, a retrospective review concluded it was effective in reducing pain severity or frequency in several nonmigraine headache disorders. This review included five patients with IIH and found headache days reduced from an average of 26 ± 2.9 days per month at baseline to 6 ± 4 days after 12 months of use.[36] Like the calcitonin gene–related peptide antagonists, prevention with botulinum toxin is a highly attractive option because of its efficacy in migraine, lack of interactions with diuretics or other drugs patients may be using concurrently such as antidepressants, weight-neutral status, and relative safety during conception, pregnancy,[37] and lactation.[38] Successful management of chronic headache with botulinum toxin is demonstrated in **CASE 7-1**.

Unlike acetazolamide, topiramate is well known to improve migraine headache symptoms and is US Food and Drug Administration (FDA) approved for this purpose. Although randomized controlled trials have never been completed for topiramate in the setting of IIH, it remains a widely considered option for papilledema control because, like acetazolamide, topiramate is a carbonic anhydrase inhibitor.[39] Rodent studies showed topiramate effectively reduces intracranial pressure.[40,41] Furthermore, a 2007 open-label, randomized pilot study compared the efficacy of topiramate versus acetazolamide in improving visual field dysfunction in 40 patients with IIH with papilledema and headache.[42] The authors found that both drugs improved visual fields at 3, 6, and 12 months without statistically significant group differences at doses ranging from 100 mg daily to 150 mg daily for topiramate and 1000 mg daily to 1500 mg daily for acetazolamide.[42] Topiramate may serve as a first choice for patients with prominent headache and mild or asymptomatic papilledema or for patients who continue to experience headache after reaching ocular remission, especially if risk factors for intracranial hypertension remain uncontrolled (eg, a patient has not reached remission weight).

Although commonly encountered in general practice, this author recommends against combining diuretics (such as acetazolamide for papilledema and topiramate for headache) because of the increased risk of combined side effects, electrolyte abnormalities, and nephrolithiasis. Beyond intracranial pressure reduction, topiramate is also an attractive choice for its weight-loss and weight-neutral status. When compared with acetazolamide, patients with IIH taking topiramate lost more weight.[42] Reproductive-aged girls and women taking topiramate should be made aware that doses greater than 200 mg can reduce the efficacy of hormonal contraceptives.[39] Topiramate should be discontinued if a patient is pregnant or planning pregnancy because of the risk of congenital birth defects.[39] This author recommends stopping immediate-release topiramate 4 days before trying to conceive based on an elimination half-life of 21 hours. A longer duration would be needed for extended-release topiramate; the half-life varies by brand.

When patients cannot use topiramate, typically because of concurrent acetazolamide use, alternative classes of weight-neutral preventives must be used. Most treatments with the highest levels of established efficacy increase the risk of weight gain; this includes beta-blockers, amitriptyline, valproate, and divalproex.[29] Valproate and divalproex especially should be avoided in female patients with IIH because of the additional risk of promoting polycystic ovarian syndrome,[29] a common comorbidity. In this author's experience, beta-blockers

KEY POINTS

- **Frequent and severe headaches promote the development of more frequent headaches over time. Prevention in patients with IIH should be started at the early stages of increasing headache frequency to prevent chronification.**
- **When choosing a preventive headache treatment in patients with IIH, clinicians should consider the medication's effect on weight, safety in conception and pregnancy, and safety profile when combined with diuretics.**
- **Erenumab is the only headache-focused treatment studied in the prevention of chronic headache in IIH.**
- **Limitations with gastrointestinal absorption, for example, in patients who have undergone bariatric surgery, should be taken into account when choosing the administration mode of treatment (ie, immediate versus extended-release tablets, injections, infusions, nasal sprays) when managing headache in patients with IIH.**

are especially helpful for targeting a pulsating or throbbing quality of headache and headaches markedly worsened by physical activity. If a patient does not have additional contraindications to using beta-blockers, namely bradycardia, heart failure, Raynaud disease, depression, or asthma (depending on severity), this author will trial a beta-blocker such as extended-release propranolol 60 mg to 120 mg at bedtime.

Selective serotonin norepinephrine reuptake inhibitors (SNRIs) venlafaxine and duloxetine should be considered for patients with IIH because they are weight neutral and have relatively high efficacy.[29] These medications may serve a second purpose in treating depression, which is prevalent in women with elevated body mass index and headache[43] and a risk factor for migraine headache progression.[23] Candesartan may be considered a weight-neutral choice for patients who are not hypotensive.[29] Some patients who benefited from but could not tolerate topiramate

CASE 7-1

A 27-year-old woman with polycystic ovarian syndrome, obesity, depression, and idiopathic intracranial hypertension (IIH) presented to the neurology clinic for a second opinion regarding venous sinus stenting. She was diagnosed with IIH with papilledema at age 21 when she developed acute-onset severe headaches and vision changes. She had been in ocular remission for 5 years on acetazolamide extended-release 500 mg 2 times per day. Despite being in ocular remission, she had headaches 25 days per month. Most days, they felt like all-over throbbing, especially with physical activity, and were associated with photophobia, phonophobia, and nausea. She did not tolerate topiramate or nortriptyline, and gabapentin was ineffective. She had read about venous sinus stenting for patients with IIH and wondered if that was an option for her. Venlafaxine could not be used because the patient was already taking fluoxetine for depression.

Extended-release propranolol 120 mg daily was started for the throbbing phenotype of chronic migraine and was effective in reducing her headache frequency to 8 days per month after 3 months of use but was not tolerated because of lightheadedness. The patient was counseled on the risks and benefits of erenumab versus botulinum toxin. She had recently become engaged and hoped to be pregnant as soon as possible after her wedding, so with this in mind, botulinum toxin was chosen instead of erenumab. After her third session of botulinum toxin injections for chronic migraine, her migraine frequency reduced to 4 to 6 days per month with no additional headache days.

COMMENT

The data clearly show that lowering CSF pressure does not treat headaches in most patients with IIH, and venous sinus stenting should not be offered in this setting. The headaches demonstrated a migraine phenotype and responded well once a preventive agent was chosen that she could tolerate long enough for an adequate therapeutic trial. Treatment choices were tailored to her headache phenotype, concurrent medications, and pregnancy plans.

may experience comparable benefit from zonisamide.[3,29] In this author's opinion, zonisamide is more often a lower-efficacy preventive, especially in the context of multiple antagonists to calcitonin gene–related peptide, and should not be an early choice. Memantine, currently approved by the FDA only for treatment of moderate to severe Alzheimer dementia, is a glutaminergic receptor antagonist with established efficacy in migraine prevention.[30] It is well tolerated,[30] and this author finds it useful in the management of headaches in patients with IIH because of its weight-neutral status.

Gabapentin and pregabalin should typically be avoided in patients with IIH, both from a weight-gain perspective and low or unestablished efficacy against migraine.[44,45] With respect to calcium channel blockers, verapamil is typically avoided because of its unestablished efficacy in migraine,[45] and caution should be taken with flunarizine despite its high efficacy because of the risk of worsening depression.[3]

Neuromodulation devices are not included in the most recent American Academy of Neurology and American Headache Society[45] guidelines for prevention of migraine, published in 2012 and being updated at the time of this publication; all except external trigeminal nerve stimulation were debuted after the formulation of these guidelines. The current landscape offers other modalities including transcranial magnetic stimulation, noninvasive vagus nerve stimulation, and remote electrical neuromodulation. These are well-tolerated and weight-neutral treatments, but they were not studied or are not approved for use in patients with implantable devices or metallic devices (shunts and stents), potentially limiting their use in the setting of IIH.[46]

Prognosis

A 2023 retrospective cohort study provided the first evidence of the importance of the headache phenotype associated with IIH and tailoring preventive choices to that phenotype independent of diuretic use.[47] This study found that patients with IIH and migraine phenotype headache had lower rates of headache improvement and headache freedom 12 months after diagnosis, including after reaching ocular remission, compared with patients with IIH and nonmigraine headache despite having similar headache frequency and severity at baseline.[47] Furthermore, a large, population-based study comparing age-matched and body mass index–matched patients with IIH and migraine found that about twice as many patients with IIH were prescribed opiate analgesics compared with patients with migraine.[48] This is an important prognosticator in the context of the earlier data establishing opiate use as a risk factor for migraine chronification.[23]

Monitoring

A subset of the patients treated in the open-label study evaluating the efficacy of erenumab in headache associated with IIH developed recurrent papilledema after experiencing weight gain, despite maintaining headache remission.[17,49] This underscores the need for continued neuro-ophthalmologic surveillance despite good control of the headache disorder.

SPONTANEOUS INTRACRANIAL HYPOTENSION

SIH is a clinical and radiographic syndrome caused by CSF hypovolemia resulting from spinal dural CSF egress. The term *hypotension* is a misnomer because the syndrome results from CSF hypovolemia. SIH causes a variety of symptoms, as

KEY POINTS

- **Topiramate may serve as a first choice for patients with prominent headache and milder degrees of papilledema because it is an effective headache and weight loss agent.**

- **Combining diuretics in patients with IIH increases the risk of adverse effects.**

- **Erenumab, eptinezumab, fremanezumab, and galcanezumab are all options for headache prevention in patients with IIH because of their high efficacy, excellent tolerability, easy adherence, lack of interaction with diuretics, and weight-neutral status.**

- **Clinicians should be aware of patients' metallic (eg, shunt, stent) status if offering neuromodulation devices for headache control in the setting of IIH.**

- **Patients with IIH and migraine phenotype headache, as opposed to nonmigraine headache, are less likely to be headache-free in the long term.**

- **Recurrence of papilledema is possible without reemergence of headache in patients with IIH, so eye examinations should be monitored even when headaches are in remission.**

discussed in this section, many of which can be addressed with accurate diagnosis and treatment.[2]

Prevalence and Typical Headache Phenotype

Headache is the most common symptom of SIH, present in 98.5% of those affected, followed by vestibulocochlear symptoms (eg, dizziness, vertigo, dysequilibrium, tinnitus, distorted hearing) in about one-half and neck or back pain in about one-third.[2] The onset of the headache disorder in the setting of SIH may be gradual and progressive or sudden or thunderclap-like and severe from onset.[50] Most often the headache is orthostatic (ie, less with recumbency and worsening after assuming an upright posture or only occurring in the latter part of the day). This orthostatic quality may be lost over time. Some patients may never have a positional aspect even from onset, and occasionally patients feel paradoxically worse in the recumbent position or during sleep.[2,50] The headache is usually bilateral and posterior but may be unilateral, in any location (eg, holocephalic, occipital, frontal, fronto-occipital, temporal),[51] and described as tightening, pulling,[50] or throbbing.[2] The presence of throbbing, particularly if photophobia and phonophobia are also present (in combination with the nausea inherent to SIH), may lead to a misdiagnosis of migraine.

Response of Headache to Disease Treatment

Unlike patients with IIH, disease-specific treatments do resolve the headache disorder in most patients with SIH, but improvement varies when considering short-term versus long-term follow-up and by treatment modality, which is typically dictated by CSF leak type. The largest meta-analysis studying the presentation, investigations, and treatment outcomes of more than 2000 patients with SIH found that 64% of patients had symptomatic improvement at least temporarily with the first epidural blood patch,[51] and although the duration of follow-up was highly variable, ranging from 72 hours to 7 years, the mean follow-up was long at 25 months. A different study focusing only on 51 patients with spinal longitudinal epidural fluid collections (type 1 leaks) found that the long-term success rate of epidural patching was only 29%.[52] In this study, most (88%) of the patients had short-term clinical improvement 1 week after patching, but this reduced to 33% at a mean follow-up duration of 6.5 months. Although some patients with active CSF leaks nevertheless remained clinically improved, 71% in this study had persistent epidural fluid collections on long-term imaging.[52] A separate study of patients who underwent surgical repair of CSF leaks found substantial early improvement in headache-related disability, but, despite overall improvement, 25% continued to have severe headache-related disability 12 months after surgery.[53] Data from a large cohort of patients with CSF-venous fistulas showed that embolization led to resolution of headache in 75%, improvement of headache in 20%, and no change of headache in 5% of patients at a mean follow-up of 15 months.[54]

Pressure-Independent Headache in the Setting of Spontaneous Intracranial Hypotension

It is well established that most patients with IIH eventually experience a chronic, pressure-independent headache syndrome. The same concept of persistent headache in patients with SIH remains to be explored. The pain and other symptoms associated with SIH are attributed to both downward traction on pain-sensitive structures caused by brain sag and venous congestion occurring as a compensation for intracranial CSF volume depletion.[55] These phenomena are unlikely to be the only mechanisms of symptoms, because up to 19% of patients with SIH have normal brain imaging[51] and patients with brain sag and venous congestion may remain asymptomatic.[56]

The data indicate that most patients with SIH have long-term resolution of symptoms when definitive leak treatment is accomplished, but a small proportion of patients remain symptomatic despite radiographic resolution of their leaks. It is not known whether these patients remain symptomatic from a persistent cryptogenic leak, an unrelated secondary headache disorder, or the development of central sensitization (akin to the IIH experience). Several authors have published the prognostic factors for poor treatment response, including normal initial brain MRI,[57] longer pretreatment duration of SIH symptoms,[54,58] a history of preexisting headache[54] or migraine,[59] and female sex.[54] These prognostic factors may hold at least some clues to the mechanisms of persistent symptoms after leak treatment.

Schievink and colleagues[57] reasoned that patients with normal initial brain MRI do not respond as well to definitive treatment because they lack the anatomic compensatory measures for CSF loss.[57] The presence of these compensatory measures (eg, venous engorgement, pachymeningeal enhancement) is thought to be an early and transient finding before other (unknown) measures take over.[54] These findings may predate symptoms altogether,[56] suggesting some other anatomical tipping point is at play in determining symptomatic status, and perhaps these mechanisms are also faulty in those who lack initial imaging findings. This transition from asymptomatic to symptomatic status warrants further study because it may hold important treatment information for these patients who remain symptomatic despite normal or normalized imaging.

The persistence of headache in those with a longer duration of symptoms before treatment, history of preexisting headache disorder, and possibly female sex may suggest the development of CSF leak–initiated central sensitization akin to observations in patients with IIH. History of headache, especially migraine, generally more common in girls and women, may signal the predisposition toward central sensitization (cortical hyperexcitability), whereas the longer duration of symptoms allows more exposure to the chemical pathways that promote central sensitization to develop and amplify. In the setting of IIH, central sensitization is thought to be triggered in part by dural sinus congestion, a result of the venous hypertension that occurs in that disorder.[18] These patients may then develop mechanical hypersensitivity at the level of the chemically sensitized dura.[19] It is possible that the same two pathways can be activated in SIH, which is also intimately tied to the dural vasculature by way of pachymeningeal enhancement, venous sinus engorgement, brain sag (ie, traction on the dura), and shares symptoms of dural mechanical hypersensitivity (eg, headache triggered by Valsalva maneuvers, meningismus).

Differential Diagnosis of Persistent Headache

Differential diagnoses of persistent headache in patients with spontaneous intracranial hypotension include the following:

- **Cryptogenic, imaging-negative leak**
- **Rebound intracranial hypertension**

KEY POINTS

- **Headache is the most frequent symptom of SIH and varies in phenotype. Some patients continue to have long-term headache despite successful radiographic treatment of their CSF leak.**

- **The mechanisms for persistent headache after treatment of SIH have not been defined. Poor headache-related prognosis was seen in patients who had normal initial brain imaging, longer durations of symptoms before CSF leak treatment, history of preexisting headache or migraine, and female sex.**

- **It remains unknown whether patients with SIH develop central sensitization via similar pathways as patients with IIH.**

- **Underlying idiopathic intracranial hypertension**
- **Postural orthostatic tachycardia syndrome**
- **Cervicogenic headache**
- **Central sensitization (tension headache or cervical myofascial pain syndrome, chronic migraine)**

First and foremost, CSF leaks may remain partially treated[52] or may reoccur at the same level or a new level after initially successful treatment.[54] This author recommends close radiographic monitoring of the leak. An updated brain MRI (with gadolinium if possible) is requested within 3 months before treatment to establish an immediate pretreatment radiographic baseline. Because there may be a delay in the complete resolution of radiographic stigmata on brain MRI even after clinically successful treatments, a repeat brain MRI (with gadolinium again if possible) is performed 1 to 3 months after treatment to evaluate for radiographic resolution of SIH. Thereafter, patients are followed clinically for a return of symptoms, which prompt repeat brain imaging if present. In this author's experience, when patients have had previous improvement or resolution of symptoms who then manifest new, even subtle, radiographic stigmata, it has always pointed to the recurrence of SIH either on radiographic (eg, spinal imaging) or clinical (eg, response to treatment) grounds. Having at least one "asymptomatic" brain MRI on file for comparison is helpful for decision-making when symptoms recur.

Patients who have had one headache disorder are not immune from developing other headache disorders, and some headache etiologies may be more relevant when considering who develops SIH. Patients with underlying connective tissue disorders are more likely to develop SIH because of preexisting dural weakness and dural ectasia.[2,55] Patients with hypermobility are also more likely to have spinal degenerative changes (a risk factor for CSF leak) at an age younger than is typical. Beyond leaks, patients with hypermobility disorders are also more prone to cervical hypermobility and postural orthostatic tachycardia syndrome (POTS), both of which may present with an orthostatic headache syndrome accompanied by neck pain and dizziness.[60] The prolonged bed rest that patients with SIH experience before they are successfully treated and while they are recovering from treatments may cause deconditioning, a risk factor for POTS. In other words, what starts as SIH may continue as a similar phenotypic syndrome of deconditioning from inactivity.

The topic of persistent symptoms would not be complete without a discussion of rebound intracranial hypertension. This is a temporary phenomenon of raised intracranial pressure affecting some patients soon after SIH treatment. The true incidence is unknown because it may be unreported by the patient and requires neurologists to have an elevated level of suspicion. It is thought to arise from the abrupt increase in intracranial pressure (not necessarily above normal range) or volume when the body has made compensatory changes or reset to a new steady state of CSF dynamics during the leak. Clinically, it is recognized as a headache phenotype different from the SIH headache (eg, frontal, frontotemporal, or holocephalic as opposed to occipital), worsening rather than improving in the recumbent position and overnight or morning time and associated with nausea, vomiting, and visual changes. Symptoms typically arise within 1 to 3 days after treatment.

Severely symptomatic patients have been found to have increased lumbar puncture opening pressure, but it is also thought that pressure may technically remain normal but be symptomatic because of the relative change from a lower pretreatment level.[61] It is a matter of debate whether later onset or prolonged persistence of rebound intracranial hypertension represents a reset CSF dynamics system or the unmasking of a previous intracranial hypertension (IIH) state.

Treatment

Assuming rebound intracranial hypertension, underlying IIH, and recurrent leak as a cause of persistent symptoms after radiographic resolution of a leak have already been excluded, this author recommends the following approach.

Testing for POTS should be considered if there is clinical suspicion (eg, orthostatic palpitations, cognitive impairment, vision changes, shortness of breath, fatigue, gastrointestinal symptoms, and anxiety). POTS is diagnosed based on a sustained heart rate increase of 30 beats/min or more (40 beats/min or greater for patients 12 to 19 years old) within 10 minutes of standing or head-up tilt in the absence of orthostatic hypotension.[62]

The patient's neck should be examined for range of motion, muscle tenderness, elicitation of latent and active myofascial trigger points, and facet loading. The patient most likely has already had cervical spine imaging, which should be reexamined for the presence of pain generators, bearing in mind that structures innervated by C1-C3 nerve roots may directly refer pain to the head. These structures include the atlantooccipital joint, atlantoaxial joint, C2-C3 facet joints, and C2-C3 intervertebral disk.[63] When the cervical physical examination supports the neck as a pain generator, conservative musculoskeletal measures may be tried first, including muscle relaxers, analgesics, hot and cold therapy, physical therapy, and myofascial trigger point injections. If no relief or insufficient relief is achieved with these measures, the patient may be referred for interventional pain management to consider diagnostic or therapeutic injections. Normal cervical imaging does not exclude cervicogenic headache, but more advanced imaging, such as hybrid single-photon emission CT (SPECT-CT), may help identify an injection target.[64]

If there is no clinical suspicion of POTS, cervical myofascial pain, or cervicogenic headache, this author recommends a trial of treating persistent headaches as a central sensitization disorder. Studies on the treatment of persistent symptoms have not been conducted, so this treatment paradigm is anecdotal. It may be helpful to offer treatments that have sometimes been shown effective in the treatment of postdural puncture headache, including occipital nerve block and sphenopalatine ganglion block. A randomized, controlled, single-blind study of 50 patients with postdural puncture headache after spinal anesthesia found that repetitive greater and lesser occipital nerve block was more effective in relieving the acute pain intensity of headache than conservative management (with bed rest, hydration, and analgesics).[65] The injection technique used in this study, an infiltrate of local anesthetics with fentanyl and clonidine injected under the guidance of neurostimulation, is not typically accessible to neurologists performing occipital nerve blocks in the inpatient or outpatient setting. A separate small study used a more accessible technique for neurologists: landmark-guided bedside occipital nerve block infiltrating local

KEY POINTS

- **Connective tissue disorders are a shared risk factor for the development of SIH, postural orthostatic tachycardia syndrome, and cervicogenic headache.**
- **A new headache phenotype that develops after SIH treatment may reflect rebound intracranial hypertension.**
- **It is not known whether the same treatments offered in postdural puncture headache (eg, occipital nerve and sphenopalatine ganglion block) are also effective in the setting of SIH-associated headache.**
- **Migrainous symptoms, regardless of the trigger, are often amenable to treatment with traditional migraine preventives.**
- **A careful CSF leak symptom inventory is critical to the clinical surveillance of symptoms after treatment of SIH, and brain MRI during a time of symptomatic improvement is helpful for future comparison if symptoms recur.**

anesthetic and dexamethasone, which resolved postdural puncture headache in two-thirds of patients.[66]

With the familiarity of greater occipital nerve block in the treatment of postdural puncture headache, it is surprising how little attention this option has been given in the treatment of SIH-related headache. A single report exists of one patient with SIH who opted against epidural blood patch in favor of occipital nerve block.[67] The patient experienced headache freedom for 4 months after a single occipital nerve block with local anesthetic and corticosteroid, later reproduced for 10 months with pulsed radiofrequency ablation of the occipital nerves.[67] The authors did not indicate whether the patient went on to have any follow-up imaging to determine whether SIH was radiographically resolved and subsequently returned; nevertheless, this is one example of successful targeting of a pain generator in the presence of a recent CSF leak. Sphenopalatine ganglion block has mixed results in the treatment of postdural puncture headache, with a meta-analysis showing very-short-term benefits over conservative treatments,[68] but the quality of the data is too low for this treatment to be recommended in evidence-based clinical guidelines.[69] Sphenopalatine ganglion block has not been studied in the treatment of SIH-related headache. If this were to be a promising treatment of chronic headache after SIH treatment, the protocol would most likely need to include repetitive blocks akin to what was studied in the prevention of chronic migraine.[70]

Beyond extrapolating from the treatment of postdural puncture headache, treatment may be tailored to the clinical characteristics of the chronic headache phenotype. Recognizing that patients with preexisting migraine have a worse prognosis after SIH treatment, it may be worthwhile to maximize the medical treatment of migraine symptoms before SIH treatment is offered. This approach would be most relevant for patients with long-standing migraine who lack optimal migraine management to begin with and who develop a symptom pattern change concerning for SIH. This scenario is demonstrated in CASE 7-2. Otherwise, a trial of prevention should be considered for anyone with persistent symptoms after presumed CSF leak resolution.

Patients with pain accompanied by migrainous symptoms, such as photophobia, phonophobia, osmophobia, nausea or vomiting, and visual motion intolerance, can be offered any traditional migraine preventive (eg, antiseizure medication, antihypertensive, antidepressant, botulinum toxin injections, or calcitonin gene receptor peptide ligand or receptor antagonist). The SNRI class of antidepressants (eg, venlafaxine and duloxetine) may be particularly useful because they have chemical properties addressing both migraine spectrum and tension spectrum (musculoskeletal) symptoms. These are "all-encompassing" treatments when the prescriber is unsure of the phenotype. Venlafaxine may be preferred because a side effect for some is increased blood pressure. This may be helpful for those patients with POTS-like orthostatic intolerance. The tricyclic antidepressants amitriptyline and nortriptyline also encompass the migraine and tension spectrum, but caution should be taken particularly at higher doses because these drugs may provoke orthostatic hypotension, defeating the purpose of treating headaches associated with orthostatic intolerance. This author uses propranolol or other beta-blockers when the headaches take on a throbbing pain, especially the physical activity–related phenotype. Finally, it remains to be studied whether antagonizing the calcitonin gene–related peptide system plays a role in treating chronic headaches after SIH. The 2021 positive trial with erenumab in the treatment of headache in patients with intracranial hypertension suggests it may be worthwhile to consider shared mechanisms for SIH.[17]

Prognosis

The long-term prognosis of chronic headaches after resolution of SIH is unknown. Most research to date has focused on the diagnosis and treatment strategies for active CSF leaks. In this author's anecdotal experience, most patients with normalized imaging have fewer symptoms and require relatively little follow-up care. Patients who continue to have symptoms despite normalized imaging may be subject to invasive and noninvasive testing and

CASE 7-2

A 50-year-old woman presented to the neurology clinic with a new daily persistent headache during an emotionally stressful but not physically strenuous time in her life. The headache was holocephalic, felt like pressure, was constant but worse in intensity in the evening, and was associated with photophobia, phonophobia, neck tightness, and high-pitched tinnitus. The headache intensity was minimally improved when she was in the supine position. She had no history of spine procedures that might have caused accidental dural puncture. Before the headache pattern change, she had long-standing migraines on 15 days per month. The headache pattern did not escalate before it abruptly became constant. She had been on several short trials of migraine preventatives with poor tolerance.

Brain MRI performed several years after the onset of the headache syndrome was normal with a Bern score of 0. MRI of the cervical, thoracic, and lumbar spine showed extensive, bilateral nerve root sleeve diverticula without an extradural fluid collection. A single, nontargeted, large-volume epidural patch helped her headache for a few days only. The patient started on a regimen of onabotulinumtoxinA for chronic migraine, and after completing 4 sessions, her headache was significantly improved in severity. It continued to be daily, but it was no longer constant, and the severity improved by 60% for most of the day. The headache still worsened in the evening, but for the first time, she could be headache free with supine rest, and the photophobia and phonophobia resolved. The patient went on to have bilateral decubitus dynamic CT myelography, which found a possible but not definite CSF-venous fistula. The suspicious site was treated with a fibrin blood patch under CT guidance. After the patch, the orthostatic and evening headache syndrome completely resolved for years. She continued to experience mild recrudescence of headache just shortly before her quarterly onabotulinumtoxinA injections were due.

COMMENT

This case demonstrates the experience of a centrally sensitized patient (with long-term chronic migraine) experiencing a CSF leak with suspicious but vague symptomatology. She experienced 100% relief of leak symptoms but only after her baseline chronic migraine was treated successfully.

procedures of unclear benefit. Future work should not only focus on the diagnosis and management of active leaks but also study the clinical characteristics of patients who continue to have symptoms, the efficacy of pressure-independent treatments (ie, occipital nerve blocks, sphenopalatine ganglion blocks, trigger point injections, oral neuromodulators, botulinum toxin, and monoclonal antibodies to the calcitonin gene–related peptide receptor or ligand) in patients who continue to have symptoms, and the clinical courses of asymptomatic patients because the transition from asymptomatic to symptomatic status may hold the clues to an unrecognized symptom generator.

Monitoring

The need for monitoring patients with persistent symptoms after SIH treatment remains to be defined. When pressure-independent treatments are used, patients should be offered a proper trial of therapeutic duration (3 months for an oral neuromodulator, 3 sessions for botulinum toxin injection). It is not known whether empiric surveillance for the return of a radiographic CSF leak is useful. A careful symptom inventory at leak baseline and shortly after treatment is recommended to determine the patient's individual leak symptoms for future comparison. For example, in the setting of pretreatment Valsalva maneuver–induced headaches, the resolution and subsequent reemergence of these headaches on the background of any other headache likely supports a recurrent leak. The same reasoning may be applied to the changing quality of tinnitus: muffled, low pitched, high pitched, and static versus pulsatile. Obtaining a posttreatment brain MRI, especially when a patient has experienced some resolution of symptoms, helps establish their "normal" brain baseline for future comparison if symptoms worsen or return.

CONCLUSION

Disorders of intracranial pressure or volume are well known to cause headaches, typically as the most common symptom. A large pool of evidence has shown that most patients with intracranial hypertension due to IIH develop a chronic pressure-independent headache syndrome, and evidence is emerging that, at minimum, strategies normally reserved for the treatment of migraine help treat the persistent headache disorder. On the contrary, most patients with SIH do not go on to develop a chronic headache, but for those who do, it is an enigmatic disorder without substantial evidence-based guidance to date. Much remains to be understood about the chronic symptoms of SIH, and the work already done in IIH may hold clues.

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DISCLOSURE

Continued from page 769

onabotulinumtoxinA, propranolol, rimegepant, and topiramate are FDA approved for the treatment of migraine); and duloxetine, greater occipital nerve block, onabotulinumtoxinA, sphenopalatine ganglion block, and venlafaxine for the treatment of spontaneous intracranial hypotension-related headache (none of which are FDA approved for this purpose).

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Clinical Features and Diagnosis of Normal Pressure Hydrocephalus

By Abhay R. Moghekar, MBBS

ABSTRACT

OBJECTIVE: **This article serves as a practical guide for the assessment of patients with suspected idiopathic normal pressure hydrocephalus (NPH).**

LATEST DEVELOPMENTS: **Significant advancements in neuroimaging, biomarker identification, and neurosurgical techniques have considerably improved the diagnostic accuracy and outcomes of treatment for idiopathic NPH. The full triad of gait disturbance, cognitive impairment, and urinary incontinence is not present in all patients and is not a prerequisite to pursuing treatment. Comorbid cervical stenosis is common and may also require surgical intervention.**

ESSENTIAL POINTS: **NPH remains a challenging clinical entity with significant overlap in presentation with other neurodegenerative disorders such as Alzheimer disease, vascular dementia, and parkinsonian syndromes, especially progressive supranuclear palsy and dementia with Lewy bodies. Gait tends to be affected first and more severely than other domains in patients with idiopathic NPH. The CSF tap test is a key diagnostic tool where both objective and subjective improvements in symptoms help identify patients likely to have a good outcome after shunt surgery.**

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UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE: Dr Moghekar reports no disclosure.

INTRODUCTION

Normal pressure hydrocephalus (NPH) is a clinical syndrome characterized by the triad of gait apraxia, cognitive impairment, and bladder dysfunction in the radiographic context of ventriculomegaly and normal intracranial pressure. Each cardinal feature has a long list of possible causes. Accurate diagnosis requires consideration of clinical and imaging signs, complemented by tests to exclude common mimics. Appropriate selection of patients with NPH for CSF diversion surgery adds another layer of complexity to the management of this syndrome. This article reviews the epidemiology, neuropathology, genetics, clinical features, and diagnosis of NPH, including emerging CSF biomarkers. Accompanying articles in this issue of *Continuum* discuss the radiographic evaluation and surgical treatment considerations in more detail.

EPIDEMIOLOGY

One of the earliest studies to investigate the epidemiology of idiopathic NPH at a population level found the incidence and prevalence in Norway to be 5.5 in 100,000 per year and 21.9 in 100,000, respectively.[1] A systematic review conducted in 2020 found that the prevalence of probable NPH was 10 to 22 in 100,000 and 29 in 100,000 for possible NPH. There was an age-associated increase from 3.3 in 100,000 in people aged 50 to 59 years to 5.9 in 100,000 in people 80 years old and older.[2] Results from incidence studies reported overall crude rates ranging from 1.8 to 7.3 in 100,000 per year, and age-specific rates ranging from 0.07 in 100,000 per year in people younger than 60 years old to 1.2 in 1000 per year in people 70 years old and older. If the prevalence of idiopathic NPH in the United States is the same as in reported studies, then based on US census data, approximately 700,000 people in the United States may have idiopathic NPH.[3] One limitation of these epidemiologic studies is ascertainment bias because NPH is frequently misdiagnosed. More recently, a 2024 population-based imaging study reported a prevalence of idiopathic NPH of 1.5% among 70-year-old patients, which is considerably higher than that reported earlier for this age group.[4] This study also found that imaging signs consistent with NPH were even more prevalent in this population (5.1%).

KEY POINT

- **Normal pressure hydrocephalus (NPH) is more prevalent than previously thought, with estimates of approximately 700,000 affected individuals in the United States. Its incidence increases with age.**

SOCIETAL COSTS

Managing the population of patients with NPH, including those with and without CSF diversion, places considerable financial and nonfinancial burden on individuals, families, and society. A study of Medicare beneficiaries with idiopathic NPH in the United States through 1999 showed that shunt surgery offered symptom improvement and reduced spending overall.[5] A follow-up study in 2019 demonstrated higher costs overall and that surgical treatment had become the more expensive approach.[6] Another study showed that patients who responded to shunt surgery gained 6.2 quality-adjusted life-years, roughly equivalent to the gains from coronary artery bypass and breast cancer surgery.[7] In the Japanese SINPHONI and SINPHONI-2 multicenter trials, ventriculoperitoneal and lumboperitoneal shunting were cost-effective after 18 and 21 months, respectively, for treating patients with idiopathic NPH.[8]

CSF PHYSIOLOGY

It has traditionally been taught that CSF is secreted by the choroid plexus in the lateral, third, and fourth ventricles and driven by convection from the lateral to the third ventricle, through the fourth ventricle into the subarachnoid space, and absorbed by the arachnoid granulations at the convexity of the brain into the venous sinuses. Modern imaging techniques and in vivo experiments in animals have suggested alternative mechanisms. CSF absorption is now thought to occur also through cerebral lymphatics, via periarterial and perivenular channels, and via olfactory and spinal pathways. The precise contribution of conventional versus alternative pathways remains controversial. Phase-contrast MRI studies in humans also show pulsatile mixing of ventricular and subarachnoid CSF in the cranial and spinal compartments as opposed to a smooth convective unidirectional flow as originally postulated. Nevertheless, the conventional model for CSF circulation remains of clinical importance because it informs the key distinction between hydrocephalus that is communicating from that which is obstructive. NPH is often classified as idiopathic NPH or secondary NPH depending on the absence or presence of inciting factors, such as subarachnoid hemorrhage or aqueductal stenosis; for further information on classification of NPH, refer to Figure 9-2 in the article "Radiographic Evaluation of Normal Pressure Hydrocephalus" by Petrice Cogswell, MD, PhD, and Aaron Switzer, MD, MSc,[9] in this issue of *Continuum*.

The most common sites of obstruction are the cerebral aqueduct and the outlets of the fourth ventricle. As elaborated later in this article, some patients presenting in midadulthood may have obstructive hydrocephalus from aqueductal stenosis, and these patients tend to do well with endoscopic third ventriculostomy (an opening created in the floor of the third ventricle to bypass the obstructed aqueduct) rather than shunt surgery. A large-volume lumbar puncture is relatively contraindicated for someone with complete aqueductal obstruction. It is important to confirm that patients with suspected NPH truly have communicating hydrocephalus before invasive testing with a large-volume lumbar puncture or extended lumbar CSF drainage.

ETIOPATHOGENESIS

A single unified theory is lacking to explain ventriculomegaly in the presence of relatively normal static intracranial pressures; the selective and characteristic involvement of gait, cognition, and urinary dysfunction; and the dramatic and immediate response to a lumbar puncture and eventually shunt surgery. Different pathways of altered CSF dynamics may result in a common and identifiable phenotype that responds to CSF diversion whether by a large-volume lumbar puncture, extended lumbar drainage, or shunt surgery. Alterations in biomechanical properties of the brain parenchyma, abnormal CSF hydrodynamics, changes in cerebral blood flow (with the attendant vascular risk factors), and congenital factors have all been postulated, supported by varying degrees of in vivo observations and limited experimental evidence.[10]

CSF Hydrodynamics

The earliest theory of idiopathic NPH postulated a gradual impairment in CSF absorption (ie, increased CSF outflow resistance as measured by infusion studies) resulting in the accumulation of CSF in the ventricles. This results in ventricular enlargement while keeping mean pressures constant. The resulting ventriculomegaly disproportionately affects the periventricular white matter and subcortical gray matter structures resulting in gait and subcortical cognitive impairment. More recently, based on 2021 neuroimaging studies, glymphatic dysfunction has been postulated to contribute to impaired clearance of interstitial fluid and CSF from the cranial cavity in patients with idiopathic NPH.[11]

Cerebral Blood Flow

Positron emission tomography (PET) and single-photon emission CT (SPECT) studies have shown reduced global and regional cerebral blood flow in patients with NPH, indicating impaired cerebrovascular autoregulation and ischemia in periventricular regions. Ventricular expansion in the setting of NPH also distorts the connections and blood vessels between critical brain regions such as the basal ganglia and frontal cortex. This distortion can cause deep lacunar infarctions and disrupt white matter tracts, contributing to the clinical symptoms of gait disturbances and cognitive deficits. Numerous epidemiologic studies support this hypothesis and show the high prevalence of vascular risk factors (eg, hypertension, diabetes, obstructive sleep apnea) in patients with idiopathic NPH.[12–14] Experimentally, increasing the pulse pressure with a balloon in the cerebral lateral ventricles of sheep led to ventriculomegaly within hours, and conversely, unilateral choroid plexectomy prevented the development of ventriculomegaly ipsilaterally, despite not altering mean pressures.[15]

Congenital Factors

A subset of patients with hydrocephalus present since birth are well compensated and do not manifest any dysfunction until they are in the range of 16 to 55 years old. This observation has been variously called the *syndrome of hydrocephalus in young and middle-aged adults*[16] or *long-standing overt ventriculomegaly in adults*,[17] and a significant subset of these have aqueductal stenosis or even complete aqueductal obstruction. Several studies have observed that a large head circumference relative to height is common among those who present in late life with idiopathic NPH.[18,19] More recent evidence also points to genetic factors, detailed later in this article, in a small subset of patients with idiopathic NPH, further supporting an inherited predisposition to idiopathic NPH. Whether this mechanism is mediated through altered biomechanical properties of the brain, ciliary dysfunction, or impaired neuronal migration remains to be elucidated.

Biomechanical Factors

Recent theories postulate that an increase in brain compliance and a parallel decrease in inertance (ie, a resistance to changes in CSF flow rates) contribute to the development of idiopathic NPH.[20] With an increase in brain compliance with aging in predisposed patients, the brain and ventricles can expand easily when subjected to even normal amounts of CSF and blood flow. This expansion does not significantly raise the intracranial pressure because of the system's ability to accommodate volume changes smoothly. Simultaneously, a reduction in inertance due to a loss of brain elasticity means that the system does not effectively push back against these volume changes. As a result, normal pulsations that would typically be dampened or resisted in a noncompliant or higher-inertance system can cause more significant movements and expansions within the cranial cavity. Arteriosclerosis of the arteries, particularly within the brain, can alter the transmission of pulsatile energy. When arteries are stiffer, they may not absorb pulse waves as effectively, transmitting more energy to the surrounding brain and CSF, which, in a system with reduced inertance, fails to buffer these forces adequately and results in more tissue injury.

GENETICS

Although congenital hydrocephalus has for a while been known to be influenced by a variety of genetic factors with several specific genes (eg, *L1CAM*, *MPDZ*, *CCDC88C*) identified as contributing to its development,[21] the identification of genes specific for adult-onset NPH is more recent. A segmental copy number loss of the *SFMBT1* gene was first identified in some older adult Japanese individuals with asymptomatic ventriculomegaly.[22] This variation was also confirmed in patients with shunt-responsive idiopathic NPH studied by the same group[23] and replicated in a different population.[24] Subsequently, nonsense variations in *CFAP43* encoding cilia-associated and flagella-associated proteins were described

KEY POINTS

- NPH is classified as idiopathic or secondary depending on the absence or presence of inciting factors, such as subarachnoid hemorrhage or aqueductal stenosis.
- Ventricular expansion in the setting of NPH distorts the white matter connections and blood vessels between the basal ganglia and frontal cortex, among other critical regions.
- A large head circumference relative to height in a patient with NPH may suggest underlying congenital aqueductal stenosis or obstruction even when symptoms do not present until late in life.
- Genetic variations related to cilia and flagella function have been implicated in some cases of NPH.
- The triad of gait disturbance, cognitive impairment, and urinary incontinence, along with ventriculomegaly shown on brain imaging (MRI or CT), is neither necessary nor sufficient to make a diagnosis of NPH without ancillary testing.
- Symptoms in some patients with all three elements of the NPH triad, even when accompanied by ventriculomegaly, may not be a result of NPH but rather a combination of highly prevalent disorders in older adults.

in a Japanese family.[25] Deletions and coding variants in *CWH43* have also been described in a pair of idiopathic NPH cohorts.[26,27] Additional unique genes are quite likely involved in the pathogenesis of idiopathic NPH given the higher prevalence of an enlarged head circumference in multiple idiopathic NPH cohorts.[28]

NEUROPATHOLOGY

There is a paucity of comprehensive neuropathologic reports in the existing literature beyond small cortical biopsies taken at the time of shunt implantation. The earliest neuropathologic study, in seven patients with NPH, found demyelination and degeneration of both periventricular and deep white matter with microinfarcts, especially in the frontal lobes, and moderate to severe arteriosclerosis, accompanied by focal leptomeningeal fibrosis, diminution of arachnoid granulations, and nonspecific aging processes.[29] A subsequent study of 10 patients with NPH found predominantly vascular pathology, but three of these patients also had amyloid plaques.[30] Despite a similar 2024 observation at autopsy in three patients with NPH, a pathognomonic neuropathologic signature is still lacking.[31] None will likely be found because, unlike other neurodegenerative disorders, NPH is not a proteinopathy. Idiopathic NPH may be a functional hydrodynamic disorder akin to hypertension in which end organ injury is the cause of clinical manifestations. Treatment of the underlying disordered dynamics may prevent brain injury just as treatment of hypertension prevents end organ injury.

CLINICAL FEATURES

Although historically described as a clinical triad at presentation, the full triad is neither sufficient nor necessary for the diagnosis of NPH. As outlined in **TABLE 8-1**, gait dysfunction is widely prevalent in older adults owing to a multitude of etiologies. Similarly, the prevalence of cognitive impairment increases with age, paralleling the rise in the prevalence of Alzheimer disease and vascular dementia with age. Bladder dysfunction due to pelvic floor weakness in women and benign prostatic hypertrophy in men is also common in older adults. Finally, studies have shown a steep increase in ventricular size on MRI starting in patients in their seventies in multiple population-based cohorts.[32] Thus, it is conceivable that all three elements of the triad, even when accompanied by ventriculomegaly, may not be a result of NPH but rather a combination of highly prevalent disorders in older adults. Conversely, NPH may present with gait dysfunction as the primary and only manifestation of the disorder. If there are no clear alternative etiologies that explain a patient's gait dysfunction and imaging shows features of NPH, one need not wait for the full triad to appear before initiating assessment and possible shunt surgery.

Gait Dysfunction

Gait impairment is the cardinal and often presenting symptom of NPH. It generally precedes cognitive impairment and bladder dysfunction in onset and is relatively more affected than those domains in terms of severity. The range of impairment may vary from only a subjective sensation of imbalance with normal performance on even precise instrumented measures, to more obvious classic features, and to the inability to walk even with support. Before assuming that gait dysfunction is caused by NPH, clinicians should exclude motor weakness, proprioceptive impairment, and depressed or brisk reflexes that would signal a myeloradiculoneuropathic process and perform appropriate ancillary testing (spine imaging, nerve conduction studies and EMG). In terms of sheer prevalence, knee and hip osteoarthritis, drugs that can affect balance (eg, sedatives, hypnotics, antihypertensives), presbyopia, and presbyvestibulopathy are far more common explanations than NPH for gait dysfunction in older adults.

The typical gait associated with NPH is described as broad based with feet externally rotated, shuffling with short steps, and en bloc turning (more than 2 steps for a 180-degree turn).[33,34] A characteristic, although not unique, factor of NPH gait is that it is broad based as opposed to the narrow-based gate in patients with Parkinson disease (**FIGURE 8-1**).[35] A couple of decades after the initial description of NPH, it was observed that the onset of gait abnormality before dementia predicted good surgical outcomes.[36] These characteristics overlap quite significantly, however, with those of other neurologic disorders, including Alzheimer disease and vascular dementia.[37,38] A 2023 critical review of articles related to gait dysfunction in patients with NPH found a wide prevalence of the characteristic gait features: 43% to 100% for widened stance or broad-based gait, 39% to 100% for shuffling gait, and 33% to 90% for turning en bloc.[39] Hence, although the classic descriptions of magnetic gait, gait apraxia, shuffling gait, and turning en bloc in the setting of NPH are widely recognized, there are no features that are both sensitive and specific for NPH, and no patient should be excluded for not having a “typical NPH gait.”

Prevalence of Individual Elements of the Normal Pressure Hydrocephalus Triad Resulting From Other Causes in Older Adults

TABLE 8-1

Cognitive disorders (20% prevalence of cognitive impairment at 70 years of age)

- Alzheimer disease
- Parkinson disease
- Vascular dementia
- Dementia with Lewy bodies
- Progressive supranuclear palsy
- Frontotemporal dementia

Gait disorders (40% prevalence of gait disorders at 80 years of age)

- Peripheral neuropathy
- Osteoarthritis in hips and knees
- Myelopathy
- Medications
- Vascular contributions to cognitive impairment and dementia
- Parkinsonism

Urinary dysfunction (38.5% prevalence of urinary dysfunction in men and 37% in women at 60 years of age)

- Benign prostatic hypertrophy in men
- Pelvic floor weakness in women

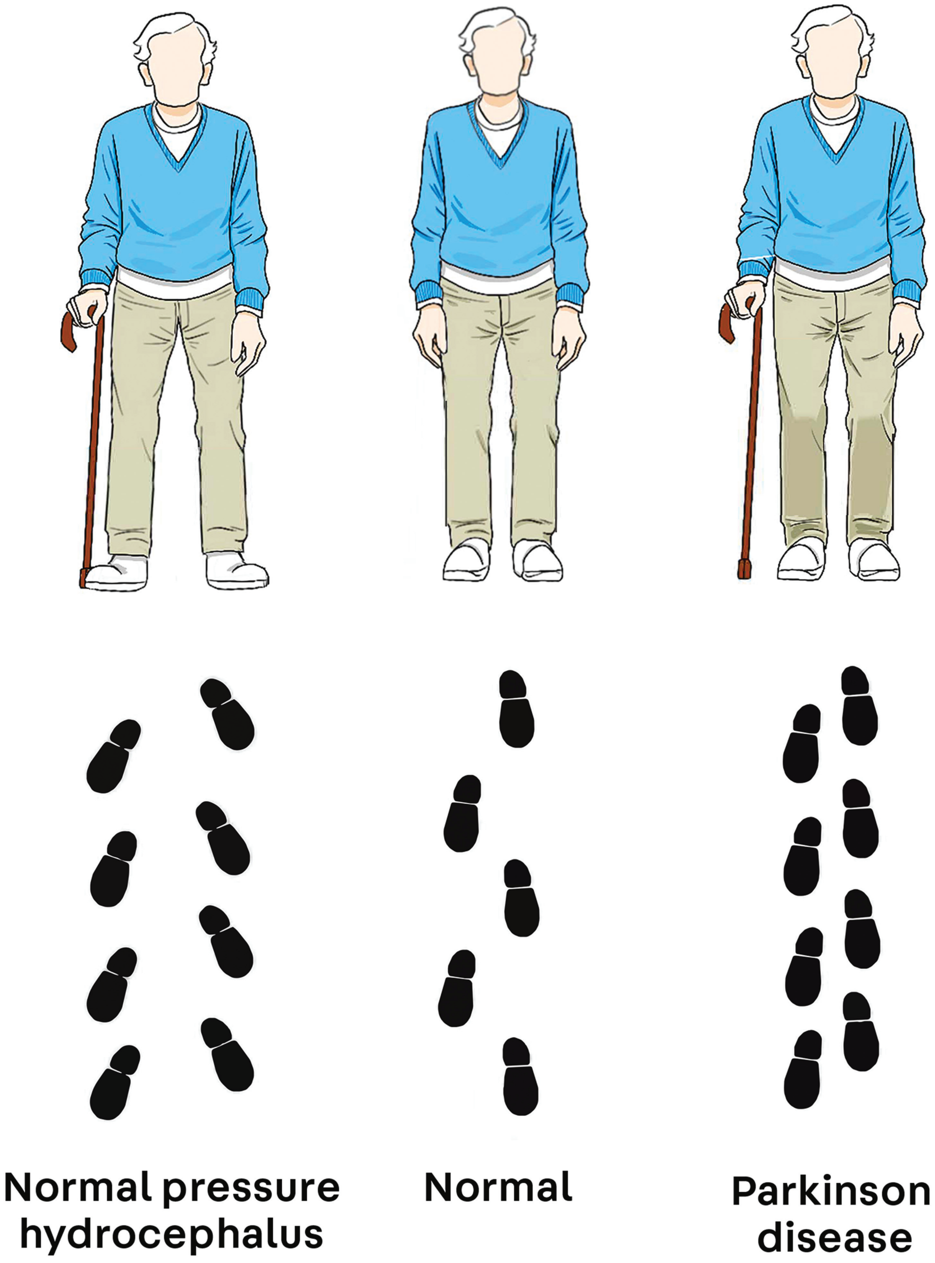


FIGURE 8-1

Gait patterns in normal pressure hydrocephalus and Parkinson disease. Gait apraxia in patients with normal pressure hydrocephalus is characterized by difficult initiation, stutter steps, short stride, slow pace, wide base, and increased steps to turn. Hypokinetic gait in patients with Parkinson disease shares some of these features but is usually narrow based.
Figure drawn by Anaya Moghekar.

Cognitive Dysfunction

NPH has been characterized as causing subcortical dysfunction, manifesting with psychomotor slowing, impaired attention, and executive dysfunction.[40] Impaired attention, memory, language, visuoperceptual, and visuospatial abilities have also all been described,[41] and a 2023 critical review failed to identify a specific cognitive profile for idiopathic NPH.[39] The range of dysfunction extends from mild cognitive impairment to advanced dementia depending on the duration of the disease before presentation, with patients who have advanced disease showing signs of cortical dementia indistinguishable from other neurodegenerative disorders. The presence of aphasia at presentation and the onset of cognitive dysfunction before gait dysfunction should prompt a search for alternative or comorbid etiologies.[42] Shunt surgery has been shown to result in improvement in global cognition, learning and memory, and psychomotor speed in multiple studies.[43,44] Although ideally a detailed neuropsychological battery may help exclude NPH mimics, at a minimum, a screening tool with sufficient assessment of the executive domain, such as the Montreal Cognitive Assessment (MoCA), may be useful.[45-47]

Bladder Dysfunction

The urinary symptoms of NPH range from mild urgency, frequency, hesitancy, and nocturia to frank urinary incontinence without awareness. A prospective evaluation of patients with idiopathic NPH showed that nearly all patients exhibited mild to moderate lower urinary tract symptoms, of which nocturia was most common. Urge incontinence was the most bothersome symptom, and 100% of patients had detrusor overactivity on urodynamic testing.[48] This observation has been corroborated in other studies of patients with idiopathic NPH.[49,50] Before ascribing all urinary symptoms to idiopathic NPH, however, one must recognize that more common conditions such as benign prostatic hypertrophy in men and pelvic floor weakness in women may also contribute to these symptoms. A separate study using [^{123}I]-iodoamphetamine SPECT showed that urinary dysfunction in patients with idiopathic NPH was closely related to right frontal hypoperfusion.[51] Although often considered a minor symptom by clinicians, patients' quality of life is often affected more by bladder dysfunction than by cognitive impairment.

Neurologic Examination

Although every patient needs to undergo a comprehensive neurologic examination at initial evaluation, particular attention must be paid to motor and other signs that may suggest an alternative or comorbid diagnosis (**TABLE 8-2**[52]).

DIAGNOSTIC TESTS

Although patients with NPH may best be managed longitudinally in a multidisciplinary setting that includes neurologists, neurosurgeons, geriatricians, neuropsychologists, and physical therapists, neurologists should feel comfortable conducting the initial evaluation. An understanding of the appropriate use of ancillary testing serves three goals: (1) to assess if there is an alternative condition that can better explain the patient's presentation (eg, cervical myelopathy, peripheral neuropathy, subcortical arteriosclerotic vascular disease); (2) to evaluate for comorbidities, especially neurodegenerative disorders that may mimic NPH or at the very least affect long-term prognosis (eg, Alzheimer disease, vascular dementia, progressive supranuclear palsy, Parkinson disease, dementia with Lewy bodies); and (3) to determine if the patient is likely to respond to shunt surgery (eg, response to large-volume lumbar puncture, extended lumbar drainage, or CSF outflow resistance testing).

KEY POINTS

- **Gait is affected before the other domains in the triad of NPH, and gait impairment is typically more severe than the cognitive or urinary impairment.**
- **No gait features are both sensitive and specific for NPH, and the diagnosis should not be excluded for the absence of a "typical NPH gait."**
- **Aphasia at presentation or onset of cognitive impairment before gait dysfunction should prompt a search for alternative or comorbid etiologies other than NPH.**
- **Quality of life for patients with NPH is often affected more by bladder dysfunction than by cognitive impairment.**
- **Upper motor neuron signs on neurologic examination should prompt evaluation for cervical stenosis, which is a common comorbidity in patients with idiopathic NPH and may require spinal decompression in up to 20% (in addition to shunt placement for idiopathic NPH).**

Guidelines

The Japanese Society of Normal Pressure Hydrocephalus and Hydrocephalus Society first elaborated guidelines for the diagnosis of idiopathic NPH in 2004 and 2005, respectively.[33,53] They classified diagnoses as definite, probable, or possible idiopathic NPH and probable, possible, or unlikely idiopathic NPH, respectively, based on a combination of imaging, clinical features, and ancillary testing. The Japanese Society of Normal Pressure Hydrocephalus guidelines have been revised twice with further details about imaging and ancillary testing.[54,55] The Hydrocephalus Society is spearheading efforts to update the 2005 guidelines given developments in testing and treatment over the past 2 decades. An American Academy of Neurology (AAN) clinical practice guideline evaluated evidence for the utility of shunting in the setting of idiopathic NPH and concluded that it is possibly effective (96% chance of subjective improvement, 83% chance of improvement on a timed walk test at 6 months) with low-level evidence (Level C) to support this recommendation.[56] In addition, it evaluated ancillary testing as predictors of shunt effectiveness and recommended that increased CSF outflow resistance (Level B) and positive response to external lumbar drainage or repeated lumbar punctures increase the likelihood of response to shunting.

Imaging

Imaging in patients with suspected NPH is discussed in the article “Radiographic Evaluation of Normal Pressure Hydrocephalus” by Petrice Cogswell, MD, PhD, and Aaron Switzer, MD, MSc,[9] in this issue of *Continuum*. Broadly, brain MRI is preferred over CT because it can evaluate multiple characteristics in addition to the basic degree of ventriculomegaly, including features specific to NPH and

TABLE 8-2

Examination Signs for Diagnosing or Excluding Normal Pressure Hydrocephalus

Finding	Comment
Large occipitofrontal head circumference	MRI should be closely examined to ensure that the hydrocephalus is communicating and not obstructive
Orthostatic hypotension	A parkinsonian disorder (eg, multiple system atrophy, dementia with Lewy bodies, Parkinson disease) or diabetic autonomic neuropathy with an accompanying large fiber peripheral neuropathy may explain gait dysfunction
Cortical cognitive impairment	Early in the course, normal pressure hydrocephalus typically manifests with subcortical dysfunction; agnosia, apraxia, aphasia, or neglect at onset raises concern for Alzheimer disease or other cortical dementia
Abnormal extraocular eye movements	Impaired vertical gaze, especially slow vertical saccades, and the presence of square-wave jerks raise the possibility of progressive supranuclear palsy
Increased or decreased muscle stretch reflexes	Hyperreflexia and other upper motor neuron signs should prompt evaluation for cervical stenosis, which may be present in up to 75% of patients with normal pressure hydrocephalus and require decompression for symptomatic myelopathy in nearly 20%[52]; reduced reflexes in the lower limbs may result from large fiber neuropathy or lumbosacral radiculopathy contributing to gait dysfunction
Rigidity with or without tremor	Increased muscle tone with or without resting tremor is expected in patients with Parkinson disease, progressive supranuclear palsy, and dementia with Lewy bodies and has also been reported in idiopathic normal pressure hydrocephalus

features that suggest alternative diagnoses. Medial temporal and hippocampal atrophy suggests Alzheimer disease, and midbrain atrophy suggests progressive supranuclear palsy. Although promising in selected cohorts, the sensitivity and specificity of the progressive supranuclear palsy–related findings have been questioned because similar midbrain atrophy has also been shown in patients with idiopathic NPH. Moreover, these additional comorbidities may be truly coincidental and do not exclude the presence of idiopathic NPH. The gait dysfunction of NPH may still be responsive to shunt surgery even though the duration of benefit may be more limited in those with comorbid pathology. The combination of Evans index, callosal angle, and disproportionately enlarged subarachnoid space hydrocephalus (DESH) provides a comprehensive radiologic assessment that aids in selecting patients with idiopathic NPH who are likely to benefit from shunt surgery. Nevertheless, clinical correlation and a holistic evaluation remain essential, as imaging findings alone may not capture the full clinical picture.

A fludeoxyglucose positron emission tomography (FDG-PET) study demonstrated that NPH was associated with global hypometabolism as opposed to the more focal temporoparietal hypometabolism of AD,[57] although more recent studies have also demonstrated more focal caudate and putamen hypometabolism.[58] Caution should be taken when interpreting focal hypometabolism in suspected NPH because it may correlate with focal CSF pockets (ie, dilated sulci) rather than true cortical atrophy or dysfunction. Although selection for shunt surgery based on amyloid-PET as a screen to exclude Alzheimer disease seemed promising, a 2021 pooled analysis demonstrated that 50% of patients with a positive scan nevertheless improved after shunting.[59] An abnormal FDG-PET should not necessarily disqualify a patient with NPH from shunt surgery, but it should inform the discussion of prognosis (ie, Alzheimer disease pattern on FDG-PET probably foretells progressive cognitive decline, but a shunt may still offer enough potential improvement in gait and mobility to consider surgery).

Before the advent of MRI, radionuclide cisternography was routinely performed to select patients for shunt surgery.[60] Persistence of tracer activity in the ventricles and a delay in the appearance of radioactivity at the superior convexity in the sagittal area on delayed scans (24 hours after injection) are considered a positive test. Currently, cisternography has limited utility in the evaluation of patients with NPH.[61]

KEY POINT

- MRI is preferred over CT for the diagnosis of idiopathic NPH. The combination of Evans index, callosal angle, and disproportionately enlarged subarachnoid space hydrocephalus (DESH) is useful in selecting patients for shunt surgery.

Large-Volume Lumbar Puncture (Tap Test)

A clinical response to draining 30 mL to 50 mL CSF via lumbar puncture is the most widely used test in selecting patients for shunt surgery. Despite this ubiquitous practice, there is little agreement on critical parameters such as the amount of CSF drained, the timing of the posttap assessment, the objective and subjective gait and cognitive measures, and most importantly, what constitutes “improvement” on these measures. Hence, it has been difficult to compare tap test utility across different studies. There is also a question about a conscious or subconscious placebo response to a procedure used to select patients for surgery.[62] The positive predictive value of the tap test is reported to be as high as 100%, although the negative predictive value may be as low as 36%.[63] Although most centers assess gait immediately before and after the lumbar puncture (given that CSF is produced at approximately 0.3 to 0.5 mL/h and will be reconstituted in less than 1 day), clinical improvement can sometimes last for days, and occasionally the greatest improvement is seen only on delayed testing. The commonly used tests are detailed in BOX 8-1, as are more sophisticated tests for specialty centers. It is important to capture quantitative measures in addition to the subjective improvement reported by patients because this establishes a useful baseline for future comparison. In addition, measures of both gait speed and balance must be administered because they are not uniformly or equally affected in individual patients and may be differentially responsive to CSF drainage and eventually shunting.

BOX 8-1

Assessing Gait in Patients With Suspected Normal Pressure Hydrocephalus

An objective measurement of gait parameters is the cornerstone of assessment in patients with suspected normal pressure hydrocephalus (NPH). Although there are many tools to assess gait, neurologists need familiarity with only a few of them to assess most patients. The choice of tests is dependent on available resources (eg, access to physical therapists) and time. In general, timed measures have higher interrater reliability.

Resource-Limited and Time-Limited Settings

Timed Up and Go: A test of gait speed and dynamic balance. It measures the time needed to walk 3 meters and back after starting from a seated position. Healthy older adults should be able to complete this in less than 12 seconds.

Dual Timed Up and Go: A test of gait and executive function. A cognitive task (serial subtractions) is performed simultaneously with the Timed Up and Go.

10-Meter Walk: A test of gait speed. This measures the time needed to walk 10 meters from a standing start. Healthy older adults should complete it in 10 seconds or less.

Four-Stage Balance Test: A test of static balance. This measures the ability to stand for 10 seconds in different conditions: feet touching each other, instep of one foot touching heel of other foot, tandem stance, one-foot stance.

Advanced Measures in Normal Pressure Hydrocephalus Specialty Clinics

NPH Scale: A 0- to 100-point scale that measures all the key features of NPH, including gait, cognition, balance, and urine control, with gait appropriately contributing double weight compared with the other domains. The gait scale incorporates the Timed Up and Go, the number of steps to complete the Timed Up and Go, and an ordinal gait scale that grades functional gait from 1 to 8. The balance scale is an ordinal scale converted to 100 points based on patients' ability to stand on one or both legs for at least 30 seconds.

Tinetti Performance Oriented Mobility Assessment: A 0- to 28-point scale that evaluates static balance and gait using ordinal measures.

Berg Balance Scale: A 0- to 56-point scale that tests static and dynamic balance.

Mini-BESTest: A 0- to 28-point scale that evaluates 14 items across four domains: anticipatory postural adjustments, postural responses, sensory orientation, and dynamic gait.

Extended Lumbar Drainage

In patients in whom a large-volume lumbar puncture results in an equivocal response and the pretest probability of NPH is high (ie, typical imaging findings, negative neurodegenerative biomarkers), some centers consider draining CSF continuously (300 mL to 600 mL total over 48 to 72 hours) via an external lumbar drain. A 2021 systematic review of four small studies showed that the positive and negative predictive values were both 90% (confidence intervals [CIs], 65% to 100% and 48% to 100%, respectively).[64] Although these values are much better than those reported for lumbar punctures, the risk of complications is also higher and includes subdural hemorrhage, meningitis, nerve root irritation, intracranial hypotension, and retained catheter fragments.[65]

CSF Outflow Resistance

CSF outflow resistance is a common tool used in Europe for evaluating patients with NPH, although it has not caught on in the United States.[66-68] Outflow resistance is often assessed via lumbar infusion tests, in which saline is infused into the CSF space and the resulting pressure changes are measured to calculate the resistance to absorption of CSF, an indirect test of the absorption failure hypothesis of NPH. The AAN guideline assigned a higher level of recommendation to outflow resistance than the more traditional lumbar puncture as a tool for selection of patients for shunting based on a pooled analysis of studies, but it noted that improvement after shunting has also been demonstrated in patients with NPH who have normal resistance outflow.[56,69,70] The European iNPH Multicentre study also showed that resistance outflow did not correlate with clinical outcomes after 12 months, so it can be a factor in selecting patients for shunt surgery but should not be used to exclude patients from treatment.

CSF Biomarkers

CSF biomarkers are becoming widely used in diagnosing Alzheimer disease and synucleinopathies (Parkinson disease, dementia with Lewy bodies) in both research and clinical practice. Their clinical implementation in the setting of NPH has been slower because the interpretation of abnormal protein levels is confounded by altered CSF hydrodynamics (eg, higher volume of distribution, impairment in glymphatic flow, turnover of CSF).[71] A pair of systematic reviews concluded that amyloid-β 42 (Aβ42), total tau, phosphorylated tau (p-tau), neurofilament light chain, and leucine-rich α-2-glycoprotein may differentiate NPH from Alzheimer disease and predict shunt responsiveness.[72,73] Although Alzheimer disease is indicated by an elevated ratio of p-tau to Aβ42, disorders of CSF dynamics such as NPH can create a pattern of abnormally low Aβ42 with normal p-tau. To the extent that CSF biomarkers can exclude alternative or comorbid neurodegenerative diseases, they can be used to predict long-term improvement in gait after shunt surgery.[74]

A stepwise algorithm for assessing patients with suspected NPH is shown in FIGURE 8-2.

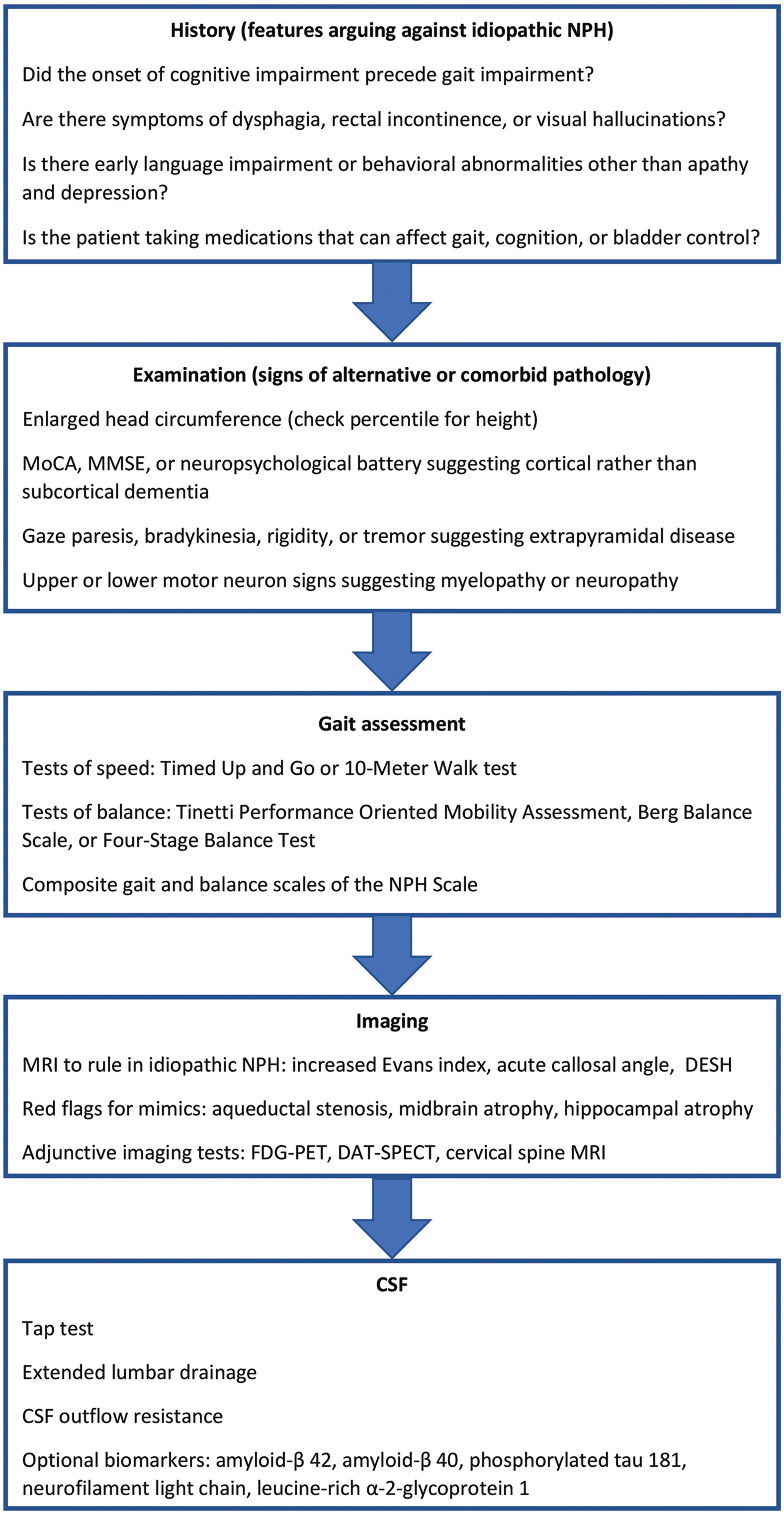
TREATMENT

The only effective treatment for idiopathic NPH is permanent CSF diversion surgery (CASE 8-1A), but not all patients will improve or experience sustained improvement. Clinical features that predict shunt responsiveness are presented in this article. Radiographic features that suggest shunt responsiveness and

KEY POINTS

- **The CSF tap test is a key diagnostic tool in which both objective and subjective improvements in symptoms after CSF removal help identify patients likely to have a good outcome after shunt surgery.**

- **Insertion of a CSF shunt is the primary treatment for idiopathic NPH. Proper patient selection can lead to significant improvement in symptoms, with an 80% chance of positive response when patients are carefully selected.**



History (features arguing against idiopathic NPH)

Did the onset of cognitive impairment precede gait impairment?

Are there symptoms of dysphagia, rectal incontinence, or visual hallucinations?

Is there early language impairment or behavioral abnormalities other than apathy and depression?

Is the patient taking medications that can affect gait, cognition, or bladder control?

Examination (signs of alternative or comorbid pathology)

Enlarged head circumference (check percentile for height)

MoCA, MMSE, or neuropsychological battery suggesting cortical rather than subcortical dementia

Gaze paresis, bradykinesia, rigidity, or tremor suggesting extrapyramidal disease

Upper or lower motor neuron signs suggesting myelopathy or neuropathy

Gait assessment

Tests of speed: Timed Up and Go or 10-Meter Walk test

Tests of balance: Tinetti Performance Oriented Mobility Assessment, Berg Balance Scale, or Four-Stage Balance Test

Composite gait and balance scales of the NPH Scale

Imaging

MRI to rule in idiopathic NPH: increased Evans index, acute callosal angle, DESH

Red flags for mimics: aqueductal stenosis, midbrain atrophy, hippocampal atrophy

Adjunctive imaging tests: FDG-PET, DAT-SPECT, cervical spine MRI

CSF

Tap test

Extended lumbar drainage

CSF outflow resistance

Optional biomarkers: amyloid-β 42, amyloid-β 40, phosphorylated tau 181, neurofilament light chain, leucine-rich α-2-glycoprotein 1

FIGURE 8-2

Diagnostic sequence for suspected normal pressure hydrocephalus (NPH).

DAT-SPECT = dopamine transporter single-photon emission computed tomography; DESH = disproportionately enlarged subarachnoid space hydrocephalus; MMSE = Mini-Mental State Examination; MoCA = Montreal Cognitive Assessment; NPH = normal pressure hydrocephalus.

preoperative and perioperative considerations surrounding shunt surgery are reviewed in the articles "Radiographic Evaluation of Normal Pressure Hydrocephalus" by Petrice Cogswell, MD, PhD, and Aaron Switzer, MD, MSc,[8] and "Management of Normal Pressure Hydrocephalus" by Kaisorn L. Chaichana, MD, and Jeremy K. Cutsforth-Gregory, MD, FAAN,[75] in this issue of *Continuum*.

CASE 8-1A

A 75-year-old woman presented to her primary care physician, who subsequently referred her to a neurologist, with a 1-year history of progressive difficulty walking and increased urinary urgency. She struggled with walking on uneven surfaces, turns, and getting out of chairs and cars and started using a cane after two falls. For 3 months, her verbal responses had been slower, and she had difficulty completing a complicated but familiar recipe. She reported increased urinary urgency and frequency, with occasional episodes of incontinence.

On examination, her Montreal Cognitive Assessment (MoCA) score was 22/30, losing points in executive and verbal memory domains. Her extraocular movements, muscle tone, power, sensation, and muscle stretch reflexes were normal. She had no resting tremor or axial rigidity. She exhibited a magnetic wide-based gait characterized by small, shuffling steps and difficulty initiating movement. She needed 6 steps to make a 180-degree turn. The 3-meter Timed Up and Go task took her 25 seconds (normal is 12 seconds or less).

Her brain MRI revealed enlarged ventricles with an Evans index of 0.38 and a few periventricular white matter hyperintensities, suggesting transependymal flow of CSF. Her callosal angle was 78°, and there were characteristics of disproportionately enlarged subarachnoid space hydrocephalus (DESH) on coronal sequences. She underwent a tap test wherein 40 mL of CSF was drained via lumbar puncture. There was an immediate improvement in her gait with her Timed Up and Go time improving to 14 seconds. She was referred for shunt surgery and underwent placement of a programmable ventriculoperitoneal shunt. Postoperative follow-up at 3 months showed marked improvement. She transitioned from using a cane to unassisted walking. Her Timed Up and Go test improved further to 10 seconds. Her MoCA score improved to 27/30. She reported a significant reduction in urinary urgency and frequency, with complete resolution of incontinence. At annual follow-up, she continued to show stable improvement in gait and cognitive functions and resumed some of her social activities, including participating in a local book club and cooking large family dinners. She and her family were pleased with her progress and regained independence.

COMMENT

Properly selected patients with idiopathic normal pressure hydrocephalus can respond well to shunt surgery. This patient had the characteristic gait apraxia and the full triad of normal pressure hydrocephalus including urinary and cognitive impairment. A key step in patient selection is objective assessment of gait immediately before and after temporary CSF removal (ie, the tap test).

CSF Diversion With Shunts

Shunt surgery is the only widely accepted treatment for idiopathic NPH, although alternative surgical interventions (eg, endoscopic third ventriculostomy), pharmacologic therapy, and even repeated lumbar punctures have been tried. Shunts can be placed in ventriculoperitoneal, ventriculoatrial, lumboperitoneal, and ventriculopleural configurations. The Hydrocephalus Society, the Japanese Society of Normal Pressure Hydrocephalus, and AAN guidelines all recommend shunt surgery in carefully selected patients with supportive ancillary testing to determine shunt responsiveness, as detailed earlier. In carefully selected patients, shunt surgery can achieve durable, long-term improvement in gait performance.[76] Despite the practice of shunt surgery for more than half a century, no large, multicenter, double-blind, randomized trials have been completed, although multiple smaller or unblinded studies have shown a significant benefit from shunt surgery in idiopathic NPH. The absence of a definitive study to demonstrate the effectiveness of shunting in idiopathic NPH is not due to a lack of effort; the lack of shunts with virtually closed settings, regulatory constraints, and the difficulty in recruiting patients who will be randomly assigned to a delayed intervention after experiencing clear subjective and objective improvement after a tap test have presented barriers.

An open-label study comparing shunt surgery to no surgery in 33 patients with idiopathic NPH showed improved cognitive and gait outcomes in the shunted group.[77] A similar, smaller, single-center pilot study in 14 patients randomly assigned to open shunt versus delayed opening of shunt (after 3 months) found improved motor (30% increase) and psychometric (23% increase) scores 3 months after shunt placement in the open-shunt group whereas the group whose shunts were not open in the first 3 months showed no improvement in any parameters.[70] In an open-label randomized trial of lumboperitoneal shunts in patients with idiopathic NPH, lumboperitoneal shunts were effective even in the group for whom shunts were delayed for 3 months compared with those who underwent shunt surgery immediately.[78] In a prospective, controlled, single-center study comparing 44 patients who underwent lumboperitoneal shunt surgery versus 34 who declined surgery, gait and cognitive testing improved in the shunted group whereas it worsened in the group who declined surgery.[79] A 2023 multicenter, randomized pilot study demonstrated the effectiveness, safety, and feasibility of a placebo-controlled trial in patients with idiopathic NPH and found a trend of gait velocity improvement in the open-shunt group versus the placebo group.[80] An ongoing National Institutes of Health (NIH)-sponsored, international, 17-center, double-blind randomized study (the PENS Trial) is expected to provide a more definitive answer by 2026.[81]

Timing of Shunt Surgery

The natural history of idiopathic NPH is a progression of symptoms, with worsening of gait, balance, and cognitive symptoms, that are only partially reversible when treatment is delayed. To maximize the benefits of shunt treatment, surgery should be performed soon after diagnosis.[82] A review that pooled six studies found that a delay in surgery resulted in a measurable deterioration in gait in as few as 3 months.[83] Although one open-label randomized trial of lumbar puncture shunts in patients with idiopathic NPH showed that the shunts were as effective in the group for whom shunts were delayed for 3 months as for those who underwent shunt surgery immediately,[78] subsequent studies have continued to demonstrate the benefit of early rather than delayed shunt surgery in patients with idiopathic NPH, even showing a mortality benefit in at least one study.[84,85]

Medications and Lumbar Punctures as Alternative Treatments

Although impairment of cerebrovascular reactivity to a challenge with acetazolamide is well described in the literature,[86,87] pilot studies in patients with idiopathic NPH have shown no more than modest benefit from low-dose acetazolamide in open-label, nonrandomized studies,[88,89] and no follow-up larger or randomized studies have been conducted to confirm the safety and efficacy of acetazolamide in these patients. Similarly, small case series have evaluated repeated lumbar punctures as a therapeutic option for those ineligible for shunt surgery and found variable benefits for up to 1 year.[90-92] This option

CASE 8-1B

Eighteen months after shunt surgery, the woman from CASE 8-1A returned to clinic reporting new-onset headaches and a subjective feeling of "fogginess" in her thinking, which she described as difficulty concentrating and slower thought processes. These symptoms were causing significant distress and affecting her daily activities. Her Montreal Cognitive Assessment (MoCA) had declined to 23/30, but her Timed Up and Go test was still 10 seconds.

Brain CT was performed because of the new symptoms and revealed the presence of a right subdural hygroma but no bleeding. To address the subdural hygroma, the neurosurgical team adjusted her shunt settings to reduce the rate of CSF drainage, raising the pressure at which the valve would open. This adjustment led to the resolution of the hygroma on follow-up CT.

Although the headache resolved, she experienced a deterioration in her gait, which became more unsteady and slow. Her Timed Up and Go test regressed to 18 seconds, indicating decreased mobility and increased risk of falls. Because of her worsening gait and the need to maintain lower intracranial pressure without risking further hygroma, hematoma, or overdrainage, a dedicated antisiphon device was added to her shunt system. This device prevents siphoning effects when patients are in an upright position and stabilizes CSF drainage.

With the antisiphon device in place and the shunt setting back to its original postoperative setting, she experienced a gradual improvement in her gait and cognitive symptoms over several months. Her Timed Up and Go test improved to 12 seconds. Her cognitive symptoms cleared, and her MoCA score improved to 26/30.

COMMENT

Ongoing follow-up every 6 to 12 months in a neurology clinic is strongly advised to ensure that shunt settings are optimized and that complications are addressed. Patients and families should be educated on signs of shunt malfunction, infection, or failure, most notably the recurrence of symptoms that had previously improved with shunting. Shunts are mechanical devices that can overdrain, underdrain, and become obstructed or infected.

seems like an intriguing choice for those who have contraindications to shunt surgery due to comorbidities, but objective and sustained benefits as well as safety and feasibility must be confirmed in prospective studies.

POSTSHUNT FOLLOW-UP

A relapse of symptoms after an initial response to shunt surgery has been reported in 20% to 70% of patients with idiopathic NPH depending on the duration of follow-up and could have a myriad of causes ranging from complications related to the shunt (eg, subdural hematoma, shunt infection, shunt overdrainage, shunt obstruction) to progression of comorbid neurodegenerative disorders.[93-95] Imaging may not always reveal the cause of patients' symptoms or, worse, may

CASE 8-1C

Five years after her initial shunt surgery for idiopathic normal pressure hydrocephalus (NPH), the same patient from CASE 8-1A and CASE 8-1B, now 80 years old, returned to clinic with concerns about progressive cognitive decline. Mental status testing revealed her Montreal Cognitive Assessment (MoCA) score had decreased from 26/30 to 18/30. Verbal memory, executive function, and visuospatial abilities were particularly affected. Her gait, however, was still improved from preshunt with a Timed Up and Go test of 12 seconds.

Given the previous episode of shunt malfunction, device failure was initially suspected. X-rays of the catheters and shunt valve (ie, a "shunt series") and brain CT confirmed the structural integrity of the shunt system. A nuclear medicine shunt patency study showed normal flow of the radiotracer into the lateral ventricles and abdominal cavity after injection into the shunt valve. For the possibility of subtle shunt malfunction, the neurosurgical team lowered the shunt setting (ie, increased drainage), but her cognition did not improve over the subsequent month.

Her brain MRI showed no significant changes in ventricular caliber or evidence of shunt overdrainage, further supporting the conclusion that the shunt system was functioning appropriately. Rather, the MRI showed bilateral hippocampal atrophy. Finally, fludeoxyglucose positron emission tomography (FDG-PET) showed temporoparietal and posterior cingulate hypometabolism highly suggestive of Alzheimer disease.

COMMENT

Cognitive decline with stable gait and balance was the first clue that this patient's new symptoms might not be caused by shunt malfunction. Mental status testing that suggested cortical (verbal memory, visuospatial function) rather than subcortical (executive function) impairment further suggested a process other than idiopathic NPH. Patients with idiopathic NPH can develop superimposed neurodegenerative diseases as they age, and this scenario underscores the importance of ongoing participation of neurologists in the care of patients with idiopathic NPH even after shunt surgery. Note that CSF biomarkers are available for Alzheimer disease but can be difficult to interpret in patients with shunts because of the altered CSF dynamics, so FDG or amyloid PET is preferred in this setting.

distract from the true etiology. As detailed in CASE 8-1B and CASE 8-1C, in the face of symptom relapse, it is reasonable to start by assessing and addressing structural and functional integrity of the shunt, but it is equally important to be cognizant of potential alternative neurodegenerative pathologies in these patients given their older age. Patients and families should be informed about the benefits and risks of shunt surgery before definitive intervention because the procedure can lead to complications; they should also learn the early symptoms that might indicate a shunt malfunction or infection after shunt implantation.

OUTCOMES

Multiple large single-center and multicenter studies have demonstrated improvement in gait measures, disability, and health-related quality of life measures in patients with NPH after shunt surgery.[96-99] A 2023 systematic review also showed health-related quality of life improved significantly within 1 year after shunt placement and improved scores across all domains for nearly 2 years after shunting, although these scores did not rise to the levels typically seen in healthy controls.[100] Other studies have failed to show improvement with longer follow-up, likely representing variability in patient selection, outcome measures, shunt-related malfunctions, and the development of age-related comorbidities.[94,101] A 2024 Cochrane review found moderate-certainty evidence that CSF shunting likely improves gait speed and disability in patients with idiopathic NPH in the short term, with more uncertainty regarding cognition, adverse events, and longer-term outcomes.[102]

FUTURE DIRECTIONS

Results of the ongoing NIH-sponsored PENS trial evaluating the real-world effectiveness of shunt surgery in patients with idiopathic NPH will help shape future larger multisite studies. Larger studies focusing on genetics may uncover even more genes related to the development of idiopathic NPH, which may lead to better animal models of this condition. Two practical factors that will also advance research in idiopathic NPH are the use of standard terminology and criteria for the diagnosis of NPH and defining what constitutes improvement in gait after lumbar puncture, lumbar drainage, and shunt surgery. The Hydrocephalus Society has taken the initiative on the former and should have a new classification system outlined later in 2025.

CONCLUSION

NPH presents a unique clinical challenge because of its apparent rarity and the similarity of its symptoms (cognitive impairment, incontinence, and gait dysfunction) to those of other neurologic diseases. As a treatable entity, the accurate diagnosis of NPH holds considerable therapeutic promise; however, the differentiation from NPH mimics necessitates a multifaceted approach that integrates clinical assessment with advanced neuroimaging techniques and potentially CSF biomarkers. The refinement of diagnosis through newer neuroimaging indices has been a significant stride forward, leading to more accurate patient selection for shunt procedures. Ongoing randomized clinical trials will hopefully establish the effectiveness of shunt surgery in patients with idiopathic NPH while also refining selection criteria for improved

KEY POINTS

- **Ongoing follow-up after shunt surgery is essential to manage potential complications and ensure optimal adjustment of shunt settings to maintain symptom control.**
- **Educating patients and caregivers about idiopathic NPH, its progression, and treatment options is crucial for managing expectations and improving quality of life.**

outcomes. Predictive, validated biomarkers that can reliably distinguish NPH from its mimics while also identifying the subset of patients with NPH with good long-term outcomes from shunt surgery could dramatically change the landscape of treatment, leading to personalized therapeutic strategies and improved prognoses. Ultimately, the balance between the potential for significant clinical improvement and the inherent risks associated with the invasive nature of shunt surgery must be carefully considered at the individual patient level.

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Radiographic Evaluation of Normal Pressure Hydrocephalus

By Petrice Cogswell, MD, PhD; Aaron Switzer, MD, MSc

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

OBJECTIVE: **Normal pressure hydrocephalus (NPH) is a clinical syndrome of a gait disorder, cognitive impairment, and urinary incontinence that also has characteristic imaging features. This article provides an overview of the radiographic evaluation and imaging features of NPH.**

LATEST DEVELOPMENTS: **Ventriculomegaly is an overarching imaging feature of NPH, although it is nonspecific. More specific imaging features have been described in association with NPH subtypes. Patients with idiopathic NPH commonly have features of ventriculomegaly, high-convexity tight sulci, and enlarged sylvian fissures. Patients with delayed-onset congenital NPH have features of marked ventriculomegaly, without extraventricular hydrocephalus, and may have stenosis or obstruction of the cerebral aqueduct. Evaluation of CSF dynamics, patterns of radiotracer uptake on positron emission tomography (PET), and patterns of brain stiffness on MR elastography can help to differentiate idiopathic NPH from secondary NPH or a neurodegenerative process.**

ESSENTIAL POINTS: **Imaging features of disproportionately enlarged subarachnoid space hydrocephalus are important to recognize as they are part of the diagnostic criteria for idiopathic NPH and aid in differentiating NPH from a neurodegenerative process. Evaluation of CSF dynamics, patterns of fludeoxyglucose (FDG) uptake, and patterns of brain stiffness may aid in the evaluation of challenging cases that lack typical clinical and structural radiographic features.**

INTRODUCTION

Normal pressure hydrocephalus (NPH) is a clinical syndrome of gait abnormality, cognitive impairment, and urinary incontinence.[1] This syndrome has several characteristic imaging features, some of which are included in the diagnostic criteria.[2] This article describes a brief history of imaging in the setting of NPH, focuses on the current assessment of the radiographic features of NPH, and summarizes newer imaging techniques on the horizon. It also discusses the multimodal radiographic evaluation of NPH including structural MRI, patterns of CSF dynamics evaluated by a variety of MR techniques, patterns of radiotracer uptake on positron emission tomography (PET), and brain stiffness on MR elastography. The

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RELATIONSHIP DISCLOSURE:
Dr Cogswell has received personal compensation in the range of $500 to $4999 for serving as a consultant for Lilly and as a medical education speaker with Kaplan, Inc, and in the range of $5000 to $9999 for serving as a medical education speaker with Eisai Co, Ltd. Dr Switzer has received personal compensation in the range of $500 to $4999 for serving on a scientific advisory or data safety monitoring board for Eisai Co, Ltd.

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Drs Cogswell and Switzer discuss the unlabeled use of intrathecal injection of gadolinium to evaluate CSF dynamics.

discussion of these radiographic features considers imaging characteristics specific to the described subtypes of NPH including idiopathic NPH and delayed-onset congenital hydrocephalus.

HISTORY OF NORMAL PRESSURE HYDROCEPHALUS IMAGING

Adams and colleagues[1] first described NPH long before the introduction of CT and MR imaging. Clinicians had to rely on invasive imaging techniques such as pneumoencephalography and radionuclide cisternography to investigate cases of suspected NPH. The pneumoencephalogram consisted of injecting a small volume of room air into the spinal subarachnoid space and manipulating the patient's body and head position to maneuver the air into the ventricles.[3] Lateral x-ray images of the skull traced the contour of the lateral ventricles and could reveal the presence of ventriculomegaly. The pneumoencephalogram lacked standardization, had severe complications and a high mortality rate, and became obsolete by the 1970s with the widespread use of CT imaging.[4]

Radionuclide cisternography succeeded the pneumoencephalogram to evaluate CSF dynamics in patients with suspected NPH. Radionuclide cisternography is a functional nuclear medicine technique that can measure the transit of CSF throughout the spinal and ventricular systems. A radiotracer, usually iodinated diethylenetriamine pentaacetic acid, is injected into the subarachnoid space in the lumbar spine, and a gamma camera measures the distribution of radiotracer at 2 to 6 hours, 12 hours, and 24 hours after injection. In a normal study, tracer activity can be detected in the basal cisterns by 1 hour after injection, followed by the sylvian fissures at 2 to 6 hours, surrounding the cerebral convexities by 12 hours, and finally in the arachnoid villi by 24 hours. Patients with NPH have an absent or delayed ascent of tracer activity about the cerebral convexities and variable reflux into the lateral ventricles by 24 hours after injection.[4] Radionuclide cisternography in patients with NPH eventually lost utility because of its invasive nature, limited diagnostic accuracy, and inability to predict shunt responsiveness.[5-8] Radionuclide cisternography is no longer recommended for the diagnosis of NPH by any major clinical practice guideline.[9,10]

STRUCTURAL IMAGING

Routine assessment of patients with NPH includes MRI to evaluate for structural features of NPH. High-resolution volumetric imaging (eg, three-dimensional T1-weighted), as typically performed in a dementia protocol for volumetric assessment, allows for multiplanar reformats and a detailed anatomic assessment. Structural features of interest include ventriculomegaly and radiographic attributes of specific NPH subtypes (eg, disproportionately enlarged subarachnoid space hydrocephalus [DESH] or delayed-onset congenital hydrocephalus).

Ventriculomegaly

Enlargement of the ventricular system is the overarching but nonspecific radiographic feature of NPH. The degree of ventriculomegaly can be assessed with several linear and volumetric measurements. The most common linear measurement is the Evans index, defined as the ratio of the greatest width of the frontal horns of the lateral ventricles to the width of the inner table of the calvarium on the same axial slice (**FIGURE 9-1A**).[11] A value greater than 0.3 is commonly used as a threshold for ventriculomegaly.[12]

The Evans index alone is sensitive but not specific for idiopathic NPH,[13] which has prompted the development of alternative measures of ventriculomegaly such as posterior callosal angle, z-Evans index, brain-per-ventricle ratio, and frontal-occipital-horn ratio. The posterior callosal angle is defined as the angle between the superior walls of the lateral ventricles that line the inferior portion of the corpus callosum (**FIGURE 9-1B**).[14] The posterior callosal angle is measured in the coronal plane at the level of the posterior commissure and perpendicular to the anterior commissure–posterior commissure line.[14] The posterior callosal angle is usually less than 90° in patients with idiopathic NPH and represents the morphologic consequence of lateral ventricle dilatation and narrowing of the sulci at the midline vertex, which is discussed later in this article.[15] The posterior callosal angle can reliably distinguish idiopathic NPH from neurodegenerative conditions such as Alzheimer disease,[15] and a callosal angle of less than 63° predicts shunt responsiveness.[14,16] An automated method for posterior callosal angle measurement was described in 2021.[17]

Because the ventricles tend to dilate superiorly rather than laterally in the setting of idiopathic NPH, measuring them in the coronal plane allows for a more specific representation of ventriculomegaly than the traditional Evans index.[18] The z-Evans index is defined as the maximum height of the frontal horns of the lateral ventricles divided by the vertical diameter of the inner table of the skull (**FIGURE 9-1C**) and has been found to predict a positive CSF tap test in patients with NPH.[18]

Another criticism of the Evans index is that it does not account for the width of the occipital horns of the lateral ventricles, which could lead to missing cases of idiopathic NPH with a more colpocephalic pattern. The frontal-occipital-horn ratio takes the average of the maximum widths of the frontal and occipital horns and divides it by the maximum width of the inner table of the skull (**FIGURE 9-1D**).[19] The frontal-occipital-horn ratio is more closely related to ventricular volume than Evans index alone, suggesting it is a more accurate measure of ventriculomegaly.[19]

The brain-per-ventricle ratio measures the amount of brain tissue above the lateral ventricles at either the anterior commissure or posterior commissure divided by the height of the ventricles (**FIGURE 9-1E**).[20] Using a cutoff value of 0.42 or greater for the z-Evans index and less than 1.0 (anterior commissure) or less than 1.5 (posterior commissure) for the brain-per-ventricle ratio can differentiate patients with idiopathic NPH from healthy controls better than the Evans index alone.[21]

These measures are widely applicable and can be performed on CT or MRI. Volumetric measures are more accurate, although not as widely accessible, because they require volumetric CT or MRI data and processing pipelines.[22,23] Although ventriculomegaly is a cardinal feature of NPH, it is also common among neurodegenerative diseases as a result of central atrophy. Some linear measures described here are more specific for NPH than the Evans index because they account for additional morphologic features beyond ventriculomegaly. The radiographic assessment of patients with NPH is further improved by evaluating specific patterns of multiple radiographic features.

KEY POINTS

- **Ventriculomegaly is an overarching, although nonspecific, feature of normal pressure hydrocephalus (NPH) commonly evaluated with linear measurements such as an Evans index value greater than 0.3.**

- **An acute posterior callosal angle is a predictor of shunt responsiveness and can distinguish idiopathic NPH from Alzheimer disease.**

- **Alternative measures of ventriculomegaly include the *z*-Evans index, frontal-occipital-horn ratio, and brain-per-ventricle ratio, which may be more specific for idiopathic NPH than the Evans index.**

- **Disproportionately enlarged subarachnoid space hydrocephalus (DESH) is defined by ventriculomegaly, high-convexity tight sulci, and enlarged sylvian fissures and is a distinct radiographic pattern of idiopathic NPH.**

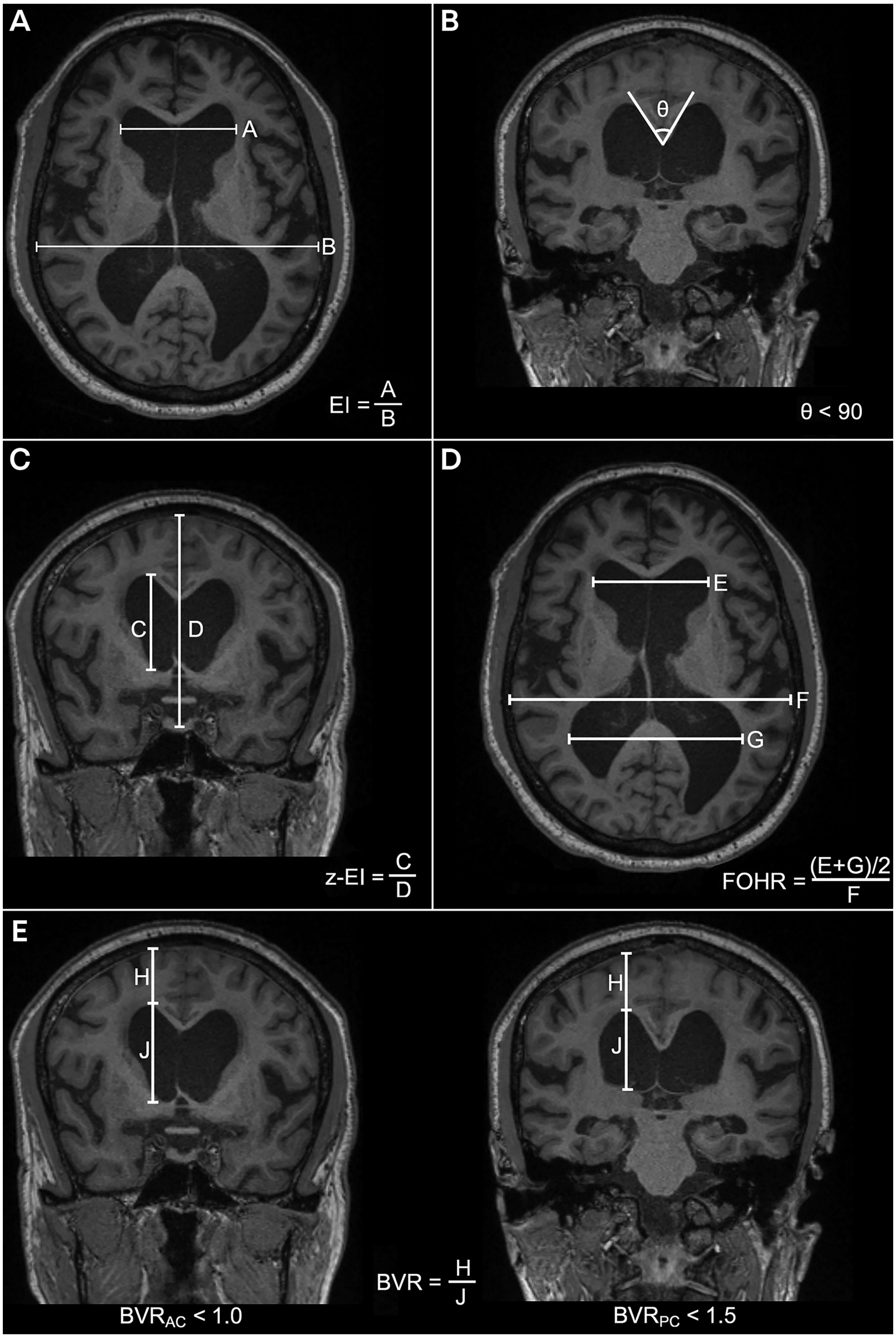

FIGURE 9-1

Linear measurements of ventriculomegaly. *A*, The Evans index (EI) is a ratio of the greatest width of the frontal horns of the lateral ventricles to the inner table of the calvarium on the same axial slice. *B*, The posterior callosal angle is the angle between the superior walls of the lateral ventricles that line the inferior portion of the corpus callosum. *C*, The z-Evans index (z-EI) is the maximum height of the frontal horns of the lateral ventricles divided by the vertical diameter of the inner table of the skull. *D*, The frontal-occipital-horn ratio (FOHR) is the average of the maximum widths of the frontal and occipital horns divided by the maximum width of the inner table of the skull. *E*, The brain-per-ventricle ratio (BVR) is the ratio of the height of parenchyma above the superior aspect of the lateral ventricle, at either the anterior commissure (AC) or posterior commissure (PC), divided by the height of the lateral ventricles.

Radiographic Patterns of Normal Pressure Hydrocephalus Subtypes

Subtypes of NPH have been described based on clinical and radiographic features.[2] One classification scheme divides NPH into idiopathic, with or without features of DESH, delayed-onset congenital, and secondary subtypes (FIGURE 9-2). This section discusses radiographic features of idiopathic NPH with DESH and without DESH, delayed-onset congenital NPH, and examples of secondary NPH.

IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS. DESH is an indirect indicator of a CSF dynamics disorder present in some patients with idiopathic NPH[24] and is predictive of shunt-responsive hydrocephalus.[25] DESH is defined by radiographic features of ventriculomegaly, high-convexity tight sulci, and enlargement of the sylvian fissures (CASE 9-1). Ventriculomegaly is most commonly evaluated via the Evans index, although multiple methods exist, as described earlier. High-convexity tight sulci have been defined as narrowing and effacement of the sulci at the midline or vertex, which is, in part, captured in the posterior callosal angle measurement. In the setting of idiopathic NPH, enlarged sylvian fissures are defined as being larger than surrounding cerebral sulci and are a sign of NPH.

Although they are not one of the three primary features of DESH, focally enlarged sulci are also present in many patients with DESH and, like enlargement of the sylvian fissures, are a manifestation of extraventricular hydrocephalus. These are cerebral sulci that are notably larger than those around them, often with globular configuration and mass effect on or distortion of the normal contour of the adjacent gyri. The adjacent sulci are often compressed, narrowed, or effaced, resulting in an unusual, nonuniform sulcal pattern (FIGURE 9-3). Common locations for focally enlarged sulci are the parieto-occipital sulcus, parafalcine sulci and longitudinal fissure, and lateral frontoparietal sulci. Focally enlarged sulci should be differentiated from atrophy or an arachnoid cyst; focally enlarged sulci occur in the setting of DESH and have outward convexal margins

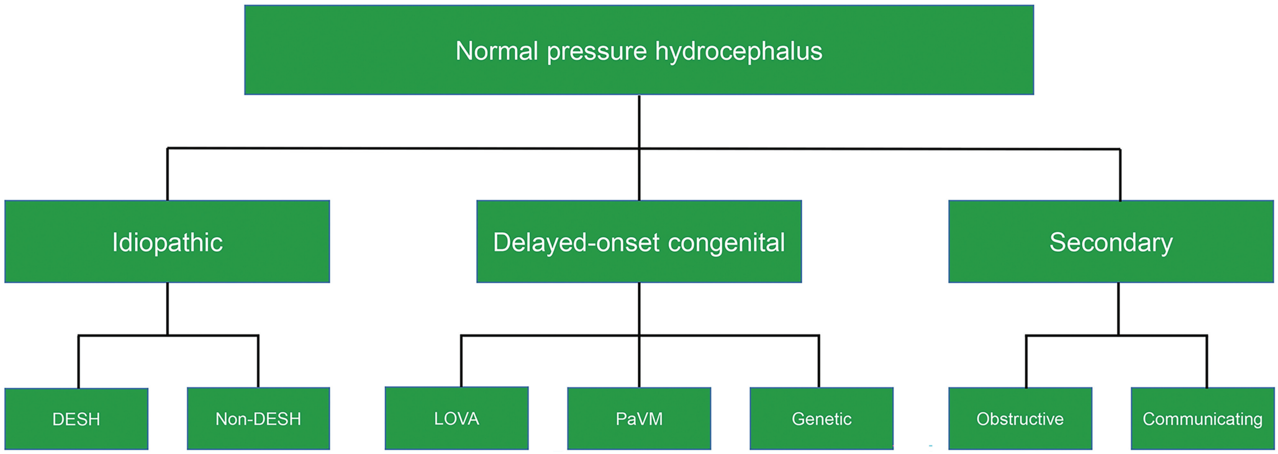

FIGURE 9-2

Normal pressure hydrocephalus subtypes.

DESH = disproportionately enlarged subarachnoid space hydrocephalus; LOVA = long-standing overt ventriculomegaly in adults; PaVM = panventriculomegaly with a wide foramen of Magendie and large cisterna magna.

and distortion of the normal sulcal pattern compared with advanced atrophy, which follows the contour of the gyrus. Several lines of evidence support that these focally enlarged sulci are a manifestation of a CSF dynamics disorder rather than atrophy. First, a case series of patients at autopsy showed the focally enlarged lateral sulci normalized when the brain was removed from the calvarium; there was no substantial atrophy.[26] Second, these focally enlarged sulci often resolve or normalize after shunt placement (FIGURE 9-3).[27] Third, patients with DESH and lack of comorbid neurodegenerative disease do not have cortical hypometabolism on fludeoxyglucose (FDG)-PET. Because NPH is a disorder of older adult patients, DESH and neurodegenerative atrophy often coexist.[28]

CASE 9-1

A 78-year-old man presented to neurology clinic with a history of mild balance problems and tripping about a decade ago. In the prior year, his gait issue became daily, and he started falling a few times a month, leading to the regular use of a walker. He also developed a right-sided more than left-sided resting tremor. Over the next 2 to 3 years, he developed progressive bladder symptoms; at first, it was intermittent urgency, followed by urgency and incontinence. He also noted cognitive decline, most prominently with poor attention and processing. He had no clear personality changes or socially inappropriate behavior. He could perform all activities of daily living independently, including finances, although he would make errors from time to time.

On examination, he scored 24/30 on the Montreal Cognitive Assessment (MoCA), losing 1 point for trail making, 1 point for the hands of the clock, 1 point for reverse digit span, 1 point for serial sevens, and 2 points for recall. He had clear parkinsonism in the form of right-sided resting tremor, asymmetric cogwheel rigidity, and bradykinesia. His gait showed a stiff upper body, reduced right arm swing, and impaired tandem steps.

Brain MRI showed a pattern of disproportionately enlarged subarachnoid space hydrocephalus, supportive of idiopathic NPH (FIGURE 9-3A, 9-3B, and 9-3C). His dopamine transporter scan was normal, arguing against a degenerative parkinsonian disorder. His gait improved after large-volume lumbar puncture. He was referred to a neurosurgeon for ventriculoperitoneal shunt placement.

Ten months after shunt placement, the patient estimated 90% improvement in his balance, had an objectively increased walking speed, and had no more falls. His MoCA score normalized to 30/30, and his urinary symptoms resolved. MRI showed a decrease in ventricular size, resolution of high-convexity tight sulci, and resolution of the enlarged extraventricular hydrocephalus (FIGURE 9-3D, 9-3E, and 9-3F).

COMMENT

This case highlights the improvements of both clinical and imaging features of idiopathic NPH after a CSF diversion procedure. It also shows how symptoms of normal pressure hydrocephalus can mimic those of a parkinsonian syndrome.

Idiopathic NPH and DESH have also been associated with more periventricular white matter hyperintensities compared with healthy people.[29-31] The white matter hyperintensities are thought to represent, at least in part, interstitial edema and transependymal flow of CSF rather than chronic small vessel ischemic changes, despite the "normal" CSF pressure.[32] More extensive white matter hyperintensities are negatively associated with clinical outcomes after shunt placement.[33]

The identification of high-convexity tight sulci and enlargement of the sylvian fissures are subjective, binary assessments of a process that occurs along a continuum; hence, there has been motivation to standardize assessment of DESH via the use of automated algorithms. Several approaches have been

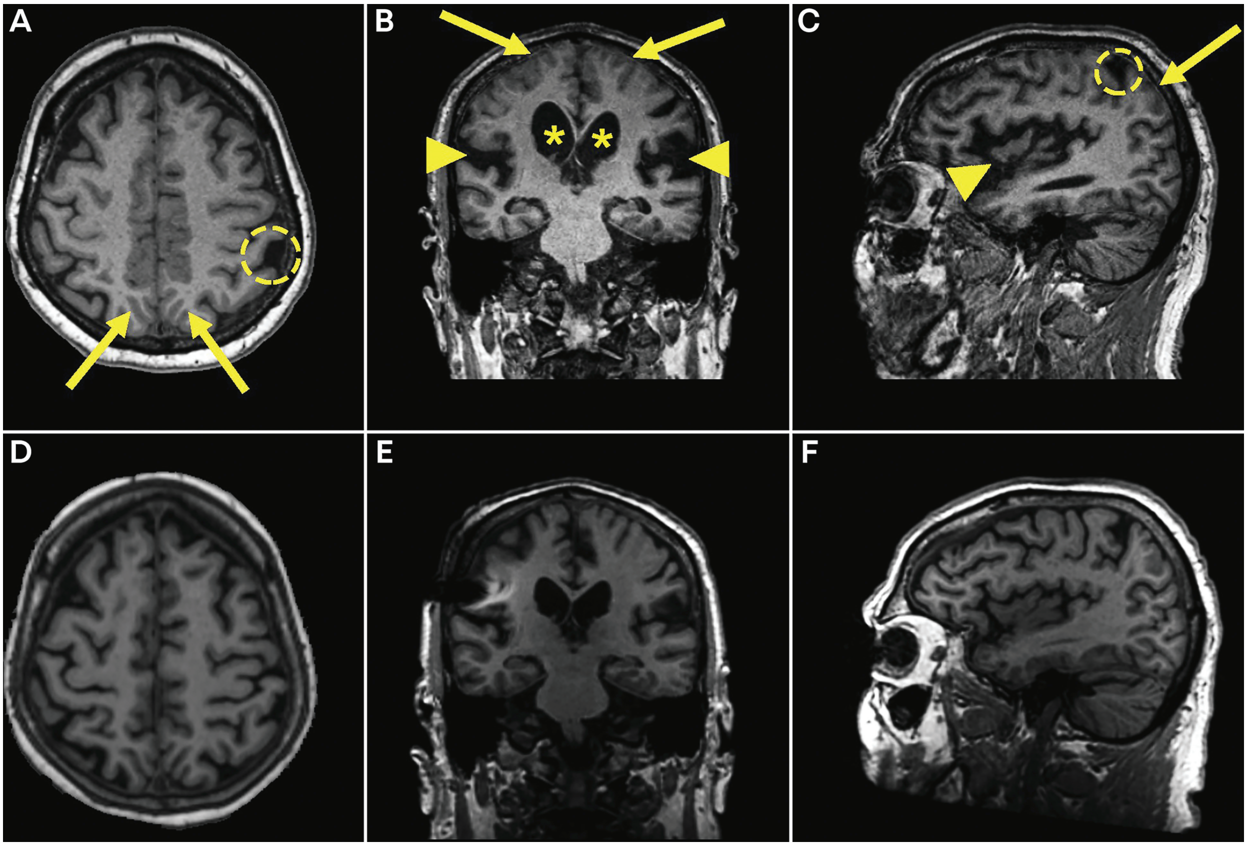

FIGURE 9-3

Imaging features of disproportionately enlarged subarachnoid space hydrocephalus (DESH) in the patient in CASE 9-1 before and after ventriculoperitoneal shunt placement. Axial (*A*), coronal (*B*), and sagittal (*C*) T1-weighted images show ventriculomegaly (*B*, *asterisks*), high-convexity tight sulci (*A-C*, *arrows*), enlargement of the sylvian fissures (*B*, *C*, *arrowheads*), and focally enlarged sulci (*A*, *C*, *dashed circle*). After shunt placement (*D-F*), the ventricles decreased in size and there was normalization of the sulcal pattern: improvement of the high-convexity tight sulci, decrease in the width of the sylvian fissures, and decrease in the size of the focally enlarged sulci.

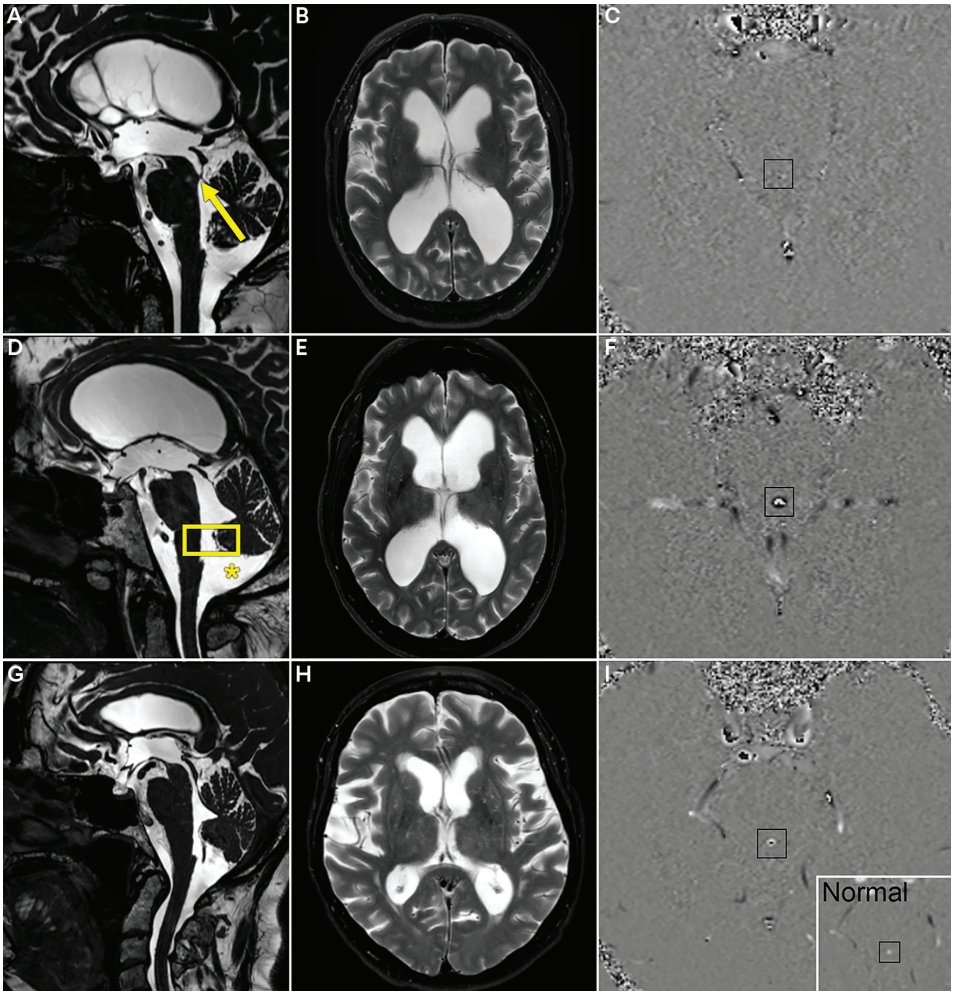

FIGURE 9-4

Arrested congenital hydrocephalus versus disproportionately enlarged subarachnoid space hydrocephalus (DESH). *A-C*, Imaging features of long-standing overt ventriculomegaly in adults (LOVA). *A*, Sagittal constructive interference in steady state (CISS) imaging shows an obstructing aqueductal web with bowing of the cerebral aqueduct above the level of the obstruction (*arrow*). *B*, Axial T2-weighted imaging shows marked ventriculomegaly (Evans index 0.47), diffusely narrowed cerebral sulci, no extraventricular hydrocephalus, and minimal periventricular white matter hyperintensities. *C*, Cine phase-contrast MRI through the level of the cerebral aqueduct (*box*) shows no appreciable flow, supporting the presence of an obstructing web. *D-F*, Imaging features of panventriculomegaly with a wide foramen of Magendie and large cisterna magna (PaVM). *D*, Sagittal CISS imaging shows a patent cerebral aqueduct, bowing of the inferior floor of the third ventricle, enlarged foramen of Magendie (*rectangle*), and enlarged cisterna magna (*asterisk*). *E*, Axial T2-weighted imaging shows marked ventriculomegaly (Evans index 0.50), diffusely narrowed cerebral sulci, no extraventricular hydrocephalus, and minimal periventricular white matter hyperintensities. *F*, Cine phase-contrast flow study through the cerebral aqueduct (*box*) shows elevated flow (average total flow, 48 mL/min; normal, 2-18 mL/min) with aliasing in the center of the aqueduct at velocity encoding of 10 cm/s. *G-I*, Imaging features of DESH, for comparison. *G*, Sagittal CISS shows a patent, uniform caliber cerebral aqueduct. *H*, Axial T2-weighted imaging shows moderate ventriculomegaly (Evans index 0.31), enlarged sylvian fissures, and narrowing of the sulci at the midline (seen posteriorly). *I*, Cine phase-contrast flow study shows flow within the upper limits of normal (average total flow, 15 mL/min) with aliasing at velocity encoding of 10 cm/s.

applied. Fully automated methods segment CSF spaces on three-dimensional T1-weighted imaging and use a support vector machine algorithm to predict an expert's classification of DESH.[34,35] Semiautomated algorithms have also been developed, which define the presence of high-convexity tight sulci as a ratio of the high-convexity sulci volume to the ventricular volume that is less than 0.6.[36]

The prevalence of DESH in the community has been evaluated by applying these algorithms and by visual assessment.[29,37-41] DESH was found in 1.0% to 6.6% of community-dwelling individuals, increased in prevalence with age, and was often asymptomatic. Features of DESH in the absence of symptoms have been termed *asymptomatic ventriculomegaly with features of idiopathic NPH on MRI* and found to be associated with development of idiopathic NPH symptoms within 3 to 5 years.[42] In community-based studies, DESH imaging features have been shown to predict future cognitive decline.[43,44]

The etiology of the morphologic features of DESH, along with the corresponding clinical symptoms of idiopathic NPH, remains unclear. It has been proposed that idiopathic NPH and these radiographic features result from disturbed CSF dynamics, including impaired CSF reabsorption (and impaired flow of CSF over the cerebral convexities), impaired CSF outflow resistance, and increased intracranial pressure pulsatility that results in gradual increases in CSF volumes in the ventricles, sylvian fissures, and major fissures.

KEY POINTS

- **Patients with DESH may have additional focally enlarged suprasylvian sulci that may be distinguished from atrophy by their outward convexal margins and surrounding narrowed or compressed sulci.**
- **DESH imaging features may occur in asymptomatic individuals and predict the development of NPH symptoms.**

DELAYED-ONSET CONGENITAL NORMAL PRESSURE HYDROCEPHALUS. Delayed-onset congenital hydrocephalus (hereafter referred to as *congenital NPH*) is a subtype of NPH in which patients are thought to have a congenital abnormality that causes hydrocephalus but does not become symptomatic until adulthood, which is reflected by the radiographic features. A few structural subtypes of congenital hydrocephalus have been described, which have in common imaging features of long-standing, compensated hydrocephalus: marked ventriculomegaly with minimal periventricular T2 hyperintensity (ie, no transependymal flow of CSF), macrocephaly, and an enlarged sella turcica (suggestive of chronic increased intracranial pressure).

One subtype of congenital hydrocephalus is long-standing overt ventriculomegaly in adults (LOVA).[45] As originally described by Oi and colleagues[45] in 2000, LOVA is characterized by macrocephaly, marked triventriculomegaly (lateral and third ventricles), and aqueductal stenosis. The aqueductal stenosis may occur as a focal narrowing or a discrete obstructing web (FIGURE 9-4). In contrast to DESH, the cerebral sulci in the setting of LOVA are diffusely narrowed or effaced, and there is no extraventricular hydrocephalus (no enlarged sylvian fissures or focally enlarged sulci). In 2017, Ved and colleagues[46] adapted the clinical and radiographic criteria for LOVA to include (1) clinical symptoms of hydrocephalus in adulthood, (2) macrocephaly, (3) overt triventriculomegaly with sulcal effacement and destruction of the sella turcica, and (4) absence of a secondary cause for aqueductal stenosis in adulthood (eg, meningitis, subarachnoid hemorrhage). Additional recommended revisions to the LOVA definition include defining *overt ventriculomegaly* as an Evans index value greater than 0.4.[47] Although the original description of LOVA included the presence of an aqueductal stenosis or web, congenital hydrocephalus has since been more widely recognized and, in some cases, occurs without an aqueductal stenosis.[48,49]

Another subtype of congenital hydrocephalus is panventriculomegaly with a wide foramen of Magendie and large cisterna magna (PaVM), which is defined by imaging features of tetraventriculomegaly (lateral, third, and fourth ventricles), patent cerebral aqueduct, wide foramen of Magendie, and enlarged cisterna magna (**FIGURE 9-4**).[50] Patency of the cerebral aqueduct was originally defined based on the presence of a flow void on T2-weighted imaging, and evaluation can now be augmented with the use of more sensitive constructive interference in steady state (CISS) or fast imaging employing steady state acquisition (FIESTA) and flow imaging (described later in this article). Some patients with PaVM have a downward bowing of the floor of the third ventricle, accompanied by septations or membranes and decreased CSF movement in the prepontine cistern. PaVM shares some radiographic features with LOVA: macrocephaly, marked ventriculomegaly, diffusely narrowed cerebral sulci, no extraventricular hydrocephalus, and minimal periventricular white matter hyperintensities. Distinct radiographic features of PaVM are the enlarged foramen of Magendie and cisterna magna. Another unique aspect of PaVM is that it has been described in families with a copy number deletion in the *DNAH14* gene, which is found in ependymal and choroid plexus epithelial cells and codes a protein involved in cilia motility.[50] This finding implicates dysfunctional cilia in the pathogenesis of this form of hydrocephalus, but the full disease mechanism remains poorly understood.[51]

Evaluation of the patency of the cerebral aqueduct is a key component of the radiographic assessment for NPH. Identification of a stenosis or web may help guide management, as some patients with an obstruction may be treated with endoscopic third ventriculostomy rather than ventricular shunt.[47-49] The presence of an aqueductal stenosis or web is best detected on high-spatial-resolution, highly T2-weighted imaging (CISS, FIESTA). These sequences are targeted for detailed anatomic evaluation and are by design insensitive to the effects of moving CSF. Evaluation of the aqueduct is complemented by flow-sensitive sequences. The presence of a flow void on standard clinical axial T2-weighted sequences supports patency of the aqueduct[52] but alone has not proven to be a useful indicator of clinical outcomes.[53] More recently, three-dimensional T2-weighted imaging techniques, such as SPACE (**s**ampling **p**erfection with **a**pplication-optimized **c**ontrast using different flip angle **e**volution), have allowed evaluation of flow voids on whole-brain volumetric acquisitions. Flow through the aqueduct can be directly measured with phase-contrast MRI, as discussed in a later section in this article. Finally, other anatomic information such as a discrepancy between the degree of enlargement of the third and fourth ventricles and bowing of the walls of the third ventricle may help support the presence of an obstruction. Integration of the information provided from each of these imaging techniques is valuable for assessing the patency of the aqueduct.

SECONDARY NORMAL PRESSURE HYDROCEPHALUS. Secondary NPH is defined by the presence of a predisposing condition, such as the presence of an obstructing tumor or impairment of CSF absorption following meningitis or subarachnoid hemorrhage. In the radiographic evaluation for NPH, it is important to evaluate for an underlying gross obstructing lesion (eg, tumor) (**CASE 9-2**) that may be causing hydrocephalus or evidence of postoperative changes causing a CSF dynamics disorder. The clinical history is also important to evaluate for previous events that may result in impaired CSF resorption or impaired CSF dynamics.

Radiographic Normal Pressure Hydrocephalus Scales

Because of the number of radiologic features of idiopathic NPH, some subjective and others objective, a standardized quantitative scale may aid the universal interpretation of CT or MRI in the diagnosis of idiopathic NPH. The iNPH Radscale was developed in 2017 to accomplish this goal.[54] The scale comprises seven different imaging findings of idiopathic NPH in which points are given for each feature and summed for a final score.[54] An iNPH Radscale score of 4 or greater corresponds to a sensitivity of 100% and a specificity of 96% for distinguishing patients with definite idiopathic NPH from asymptomatic controls.[55] Using a cutoff score of 8 or greater provides the highest probability of idiopathic NPH diagnosis with a positive likelihood ratio of 11.[55]

The Evans index is the first feature in the scale, with 2 points for an index value greater than 0.3, 1 point for an index value between 0.26 and 0.3, and 0 points for an index value of 0.25 or less.[54] High-convexity tight sulci are evaluated by using axial slices at the vertex and perpendicular coronal slices through the foramen of Monro[15]: 1 point for parafalcine sulci narrowing and 2 points for vertex sulci narrowing.[54] The sylvian fissures are assessed in a coronal plane through the center of the brainstem and sagittal planes at the midpoint between the skull and insular cortices on either side.[14] If the sylvian fissures are dilated more than the surrounding sulci, a score of 1 is given.[49] Focally enlarged sulci are evaluated in both coronal and axial planes and scored 1 if at least one is present.[54] The mean width of the maximal diameter of the temporal horns is measured in the axial plane[56] and receives a score of 2 if it is 6 mm or greater, 1 if between 4 and 5.9 mm, and 0 if less than 4 mm.[54] The posterior callosal angle is measured as described earlier in this article[14] and scored as 2 if the angle is less than 60°, 1 if the angle is between 60.1° and 90°, and 0 if the angle is greater than 90°.[54] Finally, periventricular white matter lesions are evaluated by using the Fazekas scale[49]: periventricular white matter lesions are not present (Fazekas grade 0, 0 points), thin caps around the frontal horns (Fazekas grade 1, 1 point), or confluent surrounding the lateral ventricles (Fazekas grades 2-3, 2 points).[54] Both CT and MRI can be used to accurately score each imaging feature except for white matter signal changes, which are better visualized on MRI.[57]

The iNPH Radscale has a few weaknesses that should be considered. In the population used to develop the scale, the group of patients who had responses to shunt placement was older and included more men than women than in the nonresponding group.[54] The iNPH Radscale score alone is not sufficient for predicting who will respond well to a shunting procedure.[58] The iNPH Radscale score should always be interpreted in the context of the patient's clinical symptoms of the disease (ie, gait disorder, cognitive impairment, and urinary incontinence).[55]

Change in Structural Features After Treatment With Ventriculoperitoneal Shunt

The structural features of NPH described above occur as a result of a CSF dynamics disorder and, accordingly, have been found to improve or resolve after shunt placement. The ventricular size typically decreases after CSF diversion, although to varying degrees, which may be related to the setting of the adjustable

KEY POINTS

- **Long-standing overt ventriculomegaly in adults (LOVA) is a type of congenital hydrocephalus characterized by radiographic features of marked lateral and third ventriculomegaly, relatively narrowed cerebral sulci, and a lack of extraventricular hydrocephalus, with or without aqueductal stenosis.**

- **Panventriculomegaly with a wide foramen of Magendie and large cisterna magna (PaVM) is a form of congenital hydrocephalus characterized by imaging features of lateral, third, and fourth ventriculomegaly, patent cerebral aqueduct, wide foramen of Magendie, and enlarged cisterna magna.**

- **Evaluation of the patency of the cerebral aqueduct may help guide management in patients with congenital NPH and is best performed using high-spatial-resolution, highly T2-weighted, and flow-sensitive MRI sequences.**

- **The radiographic evaluation of NPH should include evaluation for causes of secondary hydrocephalus such as tumor, previous intracranial intervention, and evidence of previous meningitis or subarachnoid hemorrhage.**

- **An iNPH Radscale score of 4 or greater corresponds to a sensitivity of 100% and a specificity of 96% for distinguishing definite idiopathic NPH from asymptomatic controls.**

CASE 9-2

A 69-year-old man presented to the neurology clinic with a 4-year history of progressive gait instability. Additionally, he described progressive cognitive impairment in the form of executive dysfunction and slower cognitive processing. He also experienced urinary frequency and incontinence. He did not endorse a history of rapid eye movement (REM) sleep behavior disorder, resting tremor, visual hallucinations, or anosmia. He lost functional independence largely because of his immobility, but he also lost the ability to drive and perform household finances independently because of his cognitive impairment. Before presenting to clinic, he completed a trial of levodopa without any improvement in his gait. He had obstructive sleep apnea that he consistently treated with continuous positive airway pressure (CPAP) therapy.

He scored 24/30 on the Montreal Cognitive Assessment (MoCA). He had no bradykinesia or rigidity on examination. His gait was slow with a magnetic quality. He displayed freezing when initiating walking, turning, and walking through a doorway. His neurologic examination was otherwise normal. MRI showed significant enlargement of the lateral and third ventricles with an Evans index value of 0.37. Severe stenosis of the cerebral aqueduct was identified on a high-spatial-resolution sagittal T2-weighted image (FIGURE 9-5). Fluid-attenuated inversion recovery (FLAIR) sequences showed expansile T2 hyperintensity of the tectal plate, most likely a low-grade glioma. The MRI showed no enlargement of the extraventricular CSF spaces, significant vascular disease, or focal pattern of atrophy. FDG-PET showed no cerebral hypometabolism. He was referred to a neurosurgeon, and the patient decided to undergo an endoscopic third ventriculostomy.

The endoscopic third ventriculostomy was successful, and the patient had an uncomplicated postoperative course. Six months after surgery, he reported significant improvement in his symptoms. He ambulated independently, his cognition had subjectively improved, and he no longer experienced urinary frequency or incontinence. His MoCA score improved to 27/30, and his gait apraxia and freezing resolved. CT at 6 months after surgery showed a slight reduction of the ventriculomegaly (FIGURE 9-5).

COMMENT

This case illustrates the importance of brain MRI in the workup for patients with normal pressure hydrocephalus to evaluate for secondary causes of ventriculomegaly. In this case, the MRI identified a tumor as the cause of the ventriculomegaly, which led to treatment with endoscopic third ventriculostomy, rather than a shunt, and an excellent clinical outcome.

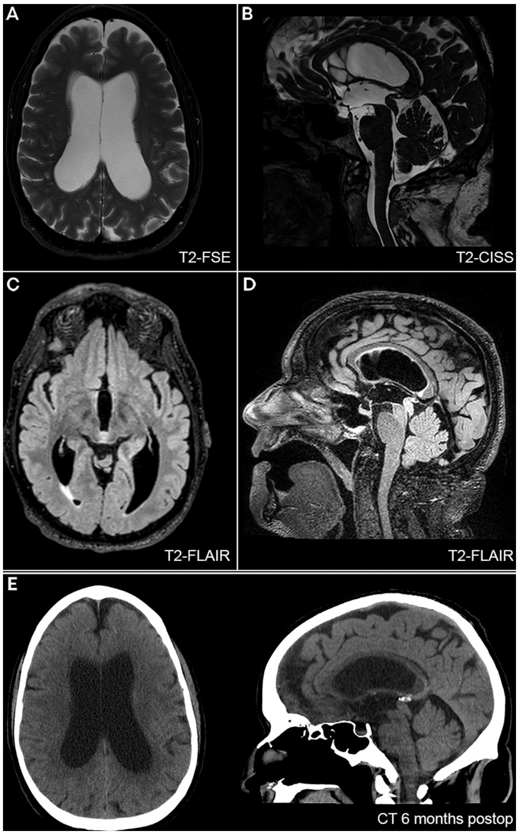

FIGURE 9-5

Imaging findings from the patient in **CASE 9-2**. Axial T2-weighted fast spin echo (FSE) sequence (*A*) shows the extent of ventriculomegaly. Sagittal T2-weighted constructive interference in steady state (CISS) sequence (*B*) shows severe stenosis of the cerebral aqueduct. Axial (*C*) and sagittal (*D*) T2 fluid-attenuated inversion recovery (FLAIR) sequences show expansile T2-hyperintense signal in the tectum likely to represent a glioma. Axial (*left*) and sagittal (*right*) CT (*E*) of his head 6 months after endovascular third ventriculostomy shows slight reduction in the ventriculomegaly.

shunt valve, underlying pathophysiology, and disease duration, among other factors. High-convexity tight sulci improve with a decrease in or resolution of the compression of the sulci at the midline vertex,[59,60] focally enlarged sulci decrease in size, and the abnormal or irregular sulcal pattern improves or resolves.[27]

CSF DYNAMICS

As discussed earlier, abnormal CSF dynamics in the setting of NPH were originally documented via nuclear medicine cisternography. Since then, multiple MR techniques have been implemented to evaluate intracranial CSF dynamics.

Phase-Contrast MRI

Elevated flow through the cerebral aqueduct has been described as an indicator of abnormal CSF dynamics in the setting of NPH. Elevated flow in the cerebral aqueduct was initially described as a flow void on T2-weighted images.[52,53] Later, cine phase-contrast MRI was implemented to directly measure the flow through the aqueduct. In this method, a two-dimensional cardiac-gated cine phase-contrast acquisition is performed to measure flow at multiple points throughout the cardiac cycle. The data are processed by placing a region of interest around the aqueduct and plotting the velocity versus time over the cardiac cycle. This should produce a sinusoidal curve, showing the cranial and caudal flow of CSF through the aqueduct during diastole and systole, respectively (**FIGURE 9-6A** and **9-6B**). From this curve, multiple metrics may be derived to characterize movement of CSF. These metrics include stroke volume, peak systolic velocity, and peak mean velocity, all of which can be elevated in patients with NPH compared with controls.[61]

The clinical utility of phase-contrast MRI has been limited for several reasons. First, elevated flow is not found in all patients with NPH; the aqueductal flow study has low sensitivity and moderate specificity for NPH.[61,62] This limitation may be related to its strong association with ventricular volume,[63] a nonspecific finding, and lack of consideration of NPH subtype (eg, DESH versus congenital NPH) in evaluation of the flow. Additionally, the studies of the association between flow through the cerebral aqueduct and shunt response have been variable, although most did not find an association.[53,64-66] Therefore, elevated flow is a supportive feature of NPH on MRI that should trigger further evaluation, but it is not part of the diagnostic criteria for NPH or for determining candidacy for treatment, and normal flow metrics do not exclude a diagnosis of NPH.

More recently, the use of phase-contrast MRI has been extended beyond imaging of a single axial slice to volumetric, four-dimensional flow techniques to study intracranial fluid movement.[67] These techniques allow for evaluation of CSF movement in three dimensions and the calculation of shear stress (**FIGURE 9-6C** and **9-6D**). The stroke volume and shear stress in the cerebral aqueduct are greater in patients with idiopathic NPH than in controls.[68,69]

Imaging of CSF flow has also been extended to real-time acquisitions, which output a continuous data stream over time rather than the average flow over the cardiac cycle.[70] These acquisitions are typically performed with a two-dimensional acquisition in the axial plane, as with the cine phase-contrast MRI aqueductal flow study, and the continuous data stream allows for determination of respiratory and cardiac contributions to aqueductal flow. These studies have shown that velocity through the cerebral aqueduct is predominantly driven by cardiac contributions, whereas the respiratory component has a greater effect on displaced volume. Simultaneous multislice echo planar imaging has been applied to obtain real-time data over a larger volume.[71] These real-time acquisitions have only recently been applied to study NPH.

Time-Spatial Labeling Inversion Pulse

Time-spatial labeling inversion pulse method (Time-SLIP) is an alternative, complementary method to phase-contrast MRI that allows visualization of the real-time movement of CSF in a single slice over a brief period (approximately 5 seconds).[72,73] The acquisition is a variant of arterial spin labeling and provides qualitative information on flow dynamics and the patency of flow between two spaces. For example, reflux of CSF from the third ventricle to the lateral ventricle

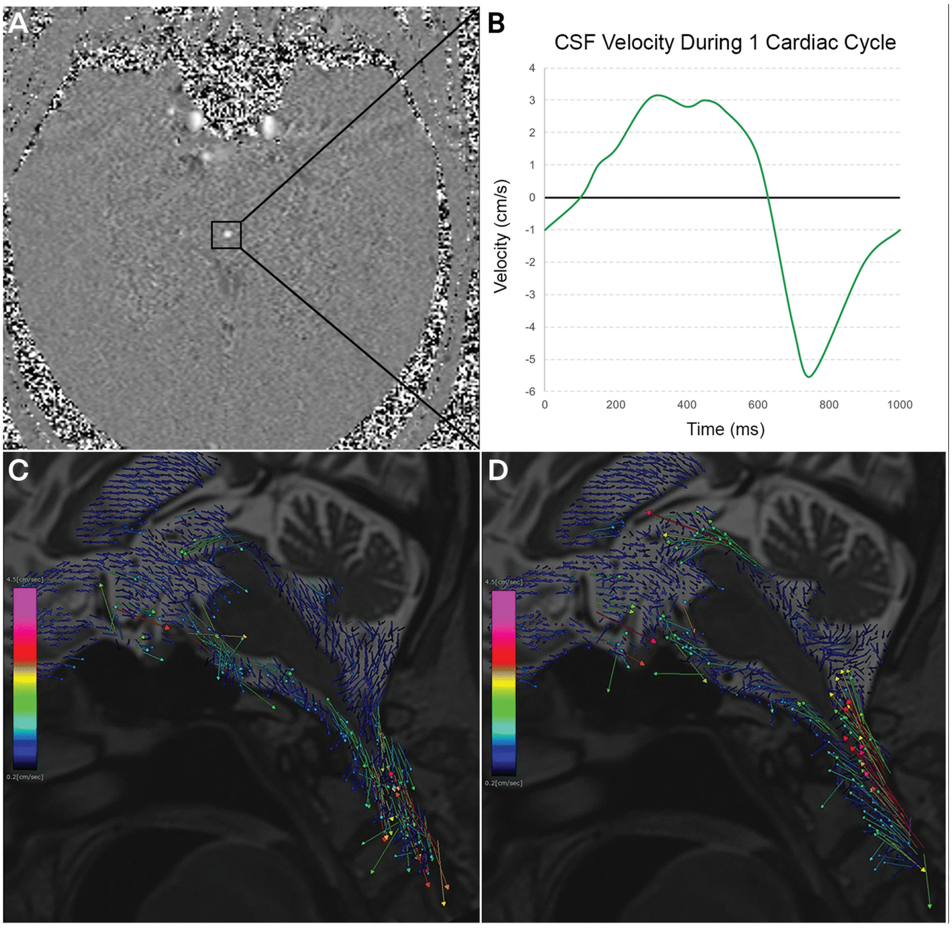

FIGURE 9-6

Imaging of CSF dynamics in the setting of normal pressure hydrocephalus (NPH). Representative images from some techniques used in clinical practice and research. Representative phase image (*A*) from a two-dimensional cine phase-contrast flow study that evaluates craniocaudal flow through the cerebral aqueduct and the processing (*B*) showing a sinusoidal velocity curve over the cardiac cycle. Four-dimensional flow study (*C, D*) that allows visualization of the movement of CSF in the *x*, *y*, and *z* directions in an imaging volume to determine flow vectors and shear stress.

Panels C and D reprinted with permission from Yamada S, et al, Eur Radiol.[68] © 2020 European Society of Radiology.

KEY POINTS

- **Imaging features of ventriculomegaly and DESH generally improve (normalize) after treatment with CSF diversion.**

- **Flow through the cerebral aqueduct is most commonly quantified by using two-dimensional phase-contrast MRI.**

- **Flow through the cerebral aqueduct is elevated in some patients with NPH. Elevated flow is a supportive feature of NPH, but its absence should not be considered evidence against NPH.**

has been shown in healthy volunteers but is reduced or not detectable in patients with NPH (**FIGURE 9-7A**). This movement of CSF between the lateral and third ventricles normalizes after ventriculoperitoneal shunt placement. Similarly, this technique may be used to evaluate patency of an endoscopic third ventriculostomy.[72]

Diffusion Imaging

Diffusion tensor imaging (DTI) is an MR technique that measures the movement of water molecules through the various tissue types of the brain.[74] Specifically, it can identify the movement of water along the axons of white matter and create elaborate maps of the white matter tracts between various cortical regions.[75] DTI can thereby assess how different neurologic conditions affect the white matter tracts. Several studies suggest that DTI analysis may be used to differentiate between patients with idiopathic NPH and controls,[76] patients with idiopathic NPH and those with Alzheimer disease,[77] and patients with idiopathic NPH who will or will not respond to shunt placement.[78]

More advanced diffusion-weighted imaging techniques have been applied to study presumed glymphatic activity by using methods such as diffusion tensor imaging analysis along the perivascular space (DTI-ALPS) and intravoxel incoherent motion. In DTI-ALPS, the data are processed to determine the ratio of diffusion along the white matter tracts at the centrum semiovale relative to diffusion in perpendicular axes. Because perivascular spaces are presumed to be primarily oriented along the white matter tracts at this location, the ratio is used as an estimate of glymphatic activity, called the *ALPS index*.[79] DTI-ALPS can accurately differentiate among patients with idiopathic NPH, those with *ex vacuo* ventriculomegaly, and healthy controls.[80] A lower ALPS index correlates with a lower callosal angle, which is a reflection of idiopathic NPH severity.[81] The same study also found that the ALPS index was significantly lower in patients with idiopathic NPH who did not respond to a shunt compared with those who did respond, suggesting that those with worse glymphatic function may have more advanced disease and be less likely to benefit from a shunt.[81] Further studies are needed to better understand the physiologic basis of the DTI-ALPS measurement.

Intravoxel incoherent motion diffusion imaging measures the brownian motion of water molecules in the intracellular, extracellular, and blood compartments of the brain as opposed to the organized motion of water molecules measured by conventional DTI techniques.[82] Studies in 2019 and 2021 used intravoxel incoherent motion–based analyses to evaluate the complex flow patterns of CSF throughout the brain.[83,84] This technique produces maps of the dynamic and complex nature of CSF flow in all areas of the brain. Of the coefficients calculated in intravoxel incoherent motion, the fraction of incoherent perfusion, or f value, is significantly lower in patients with idiopathic NPH than in controls.[85] No studies have evaluated the potential of intravoxel incoherent motion to distinguish which patients will respond to shunt placement.

Advanced diffusion MR techniques (kurtosis imaging,[86] q-space imaging,[87] and neurite orientation dispersion and density imaging[88]) have also been applied to the study of NPH. These techniques have been used as research tools to understand the underlying pathophysiology of idiopathic NPH. The techniques require 3T MRI, specific imaging parameters that add time to a clinical MRI, and, most limiting, advanced postprocessing algorithms. At present, they remain promising tools for possible future clinical use.

Intrathecal Gadolinium Imaging

Intrathecal injection of gadolinium contrast agent followed by the acquisition of serial T1-weighted MRI of the brain has also been applied to study CSF dynamics.[89] In this unlabeled technique, a minuscule amount of gadolinium contrast is injected into the lumbar thecal sac. Serial T1-weighted brain imaging is performed at set intervals over 24 to 48 hours, and enhancement is measured in

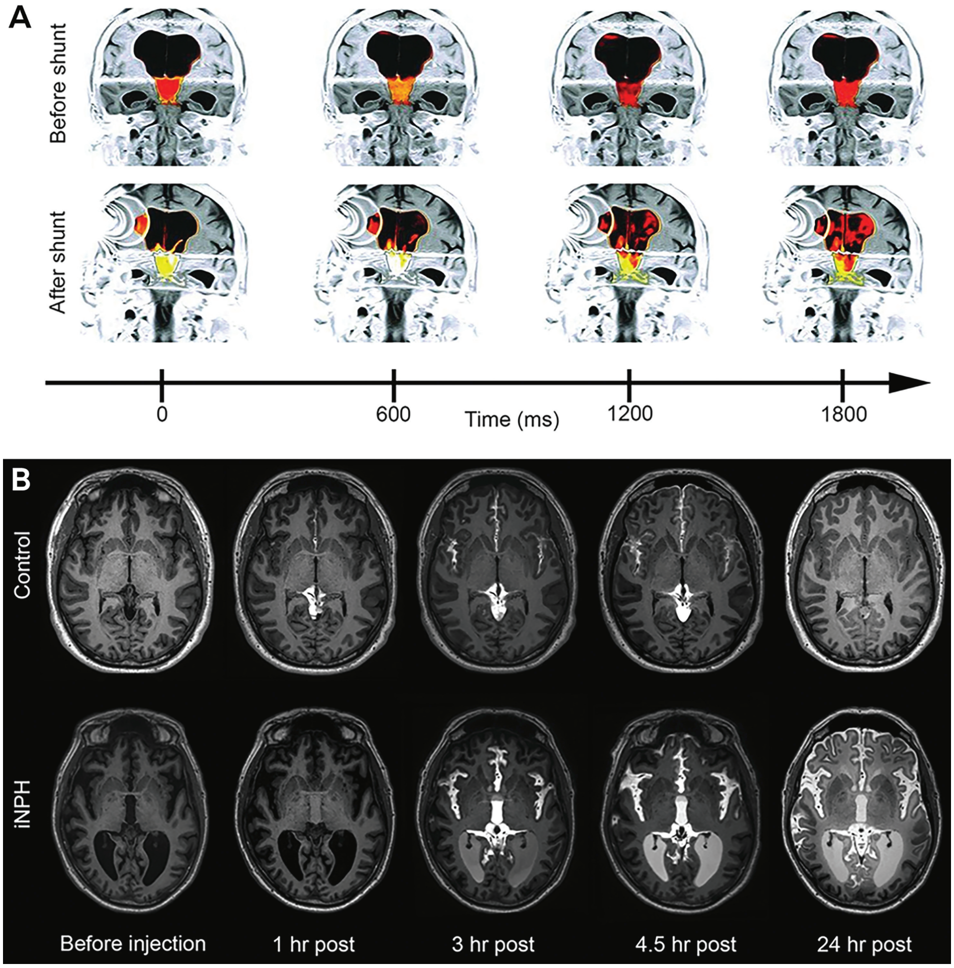

FIGURE 9-7

Imaging of CSF dynamics in the setting of normal pressure hydrocephalus (NPH). Representative images from some techniques primarily used in the research setting. *A*, Time-spatial labeling inversion pulse (Time-SLIP) allows real-time visualization of the movement of CSF in a single imaging slice. The *top row* of images shows no movement of CSF between the lateral and third ventricles in a patient with NPH. After shunt placement (*bottom row*), movement of CSF is observed between the lateral and third ventricles. *B*, Intrathecal gadolinium MRI shows distribution of intrathecal contrast through the intracranial subarachnoid spaces at 1 through 24 hours with reflux of contrast into the ventricles in a patient with idiopathic NPH (iNPH).

Panel A reprinted with permission from Yamada S, et al, AJNR Am J Neuroradiol.[114] © 2015 American Society of Neuroradiology. Panel B reprinted with permission from Ringstad G, et al, Brain.[89] © 2017 The Authors.

KEY POINTS

- **Real-time phase-contrast MRI and imaging of flow over a volume may provide further information about CSF dynamics compared with the standard two-dimensional phase-contrast MRI technique, although implementation of these more advanced techniques has to date occurred primarily within research settings.**
- **Time-spatial labeling inversion pulse (Time-SLIP) is an MRI acquisition technique that allows real-time visualization of movement of CSF in a single slice and may be used to evaluate movement of CSF between two compartments.**
- **Diffusion MRI has been applied to study white matter integrity in patients with NPH and can distinguish between NPH and neurodegenerative conditions and predict shunt responsiveness.**
- **Enlargement of the perivascular spaces can be visualized on T2-weighted MRI. Fewer enlarged perivascular spaces in the centrum semiovale in patients with NPH versus controls may result from mechanical narrowing in the setting of high-convexity tight sulci and other mechanisms.**

parenchymal, subarachnoid, and intraventricular regions of interest. In healthy patients, gadolinium has been observed to disperse progressively through the intracranial subarachnoid spaces from inferior to superior, primarily within the subarachnoid and cisternal spaces around the major cerebral arteries. Tracking of contrast movement is similar to nuclear medicine cisternography but has a higher spatial resolution. After filling the subarachnoid spaces, further imaging demonstrates progressive enhancement of the parenchyma, which is assumed to occur via contrast travel along the perivascular spaces.

In patients with NPH, compared with controls, reflux of contrast into the lateral ventricles from the subarachnoid space and subsequent transependymal enhancement have been more commonly observed.[89] Patients with NPH also demonstrated delayed enhancement and decreased clearance of contrast from the sylvian fissures and prolonged enhancement in brain parenchyma compared with controls (FIGURE 9-7B). The degree of ventricular reflux and delayed clearance are associated with structural biomarkers of NPH, Evans index, and callosal angle.[90] In patients with NPH and in controls, there was minimal to no enhancement of the convexity subarachnoid spaces. The ventricular reflux and transependymal flow suggest a small pressure gradient from the subarachnoid space to the ventricles. The delayed contrast enhancement and clearance in the setting of NPH are hypothesized to be related to reduced intracranial compliance,

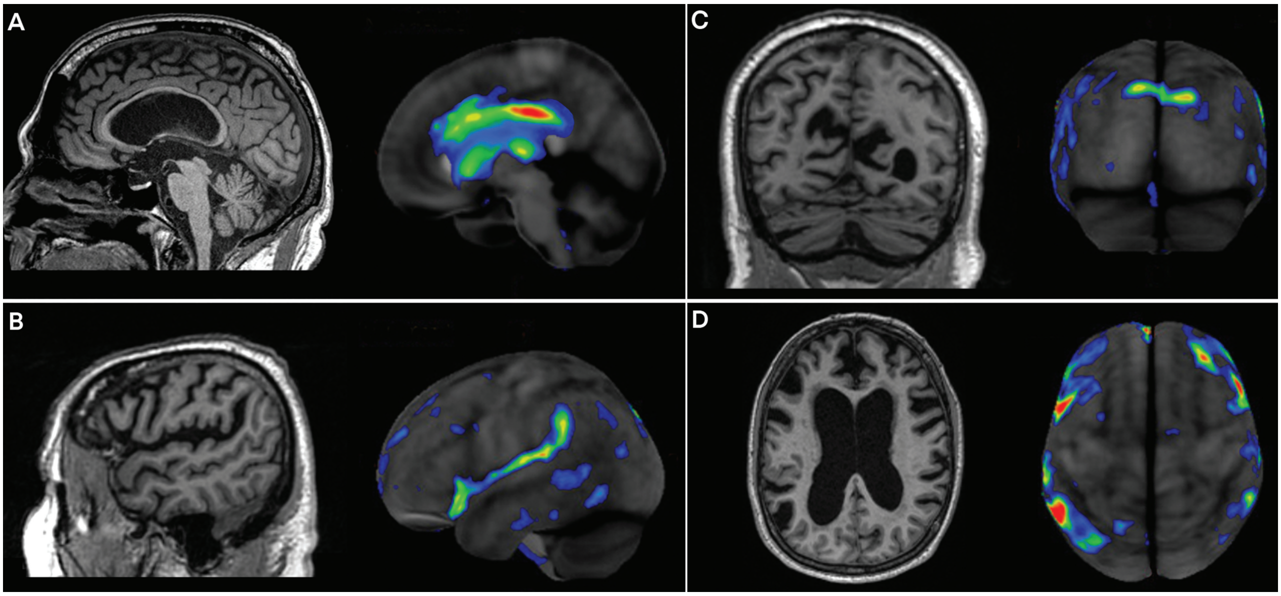

FIGURE 9-8

Fludeoxyglucose positron emission tomography (FDG-PET) in the setting of disproportionately enlarged subarachnoid space hydrocephalus (DESH) idiopathic normal pressure hydrocephalus. Representative images from T1-weighted MRI (*left*) and FDG-PET (*right*) in patients with idiopathic normal pressure hydrocephalus. The MRI shows features of DESH: ventriculomegaly (*A*), enlarged sylvian fissures (*B*), high-convexity tight sulci (*C*), and focally enlarged sulci (*C* and *D*). The FDG-PET shows regions of artifactual hypometabolism associated with the enlarged CSF spaces and is useful to show the absence of a corresponding neurodegenerative process and that the enlarged CSF spaces seen on the MRI are related to a CSF dynamics disorder rather than atrophy, as would typically have corresponding cortical hypometabolism.

which results in reduced arterial pulsations, reduced glymphatic flow, and reduced CSF transport–specifically, an obstruction of flow between the perivascular and interstitial spaces.

Intrathecal gadolinium MRI provides high spatial resolution of CSF movement and is a robust technique. Implementation is limited, however, by the need for intrathecal contrast administration, which can be performed safely[91] but is still an invasive and unlabeled technique.

Perivascular Spaces

Although not a metric of CSF movement, evaluation of the extent of perivascular space enlargement has been proposed as an indicator of glymphatic function.[92] A complex network of perivascular spaces acts as the pseudolymphatic system for the brain, and when these spaces are enlarged, they can be visualized on MRI.[93] They appear as ovoid or linear structures with the same signal intensity as CSF and are best visualized in the centrum semiovale, midbrain, and basal ganglia on T2-weighted and T1-weighted sequences.[94] Several studies have found that patients with idiopathic NPH have a specific pattern of perivascular space enlargement, whereby they have fewer perivascular spaces in the centrum semiovale and the same number in the basal ganglia compared with controls.[30,31,95] This pattern may be the result of upward displacement of the brain into the convexities or visual obscuration from increased T2 signal from transependymal CSF flow into the periventricular white matter.[31]

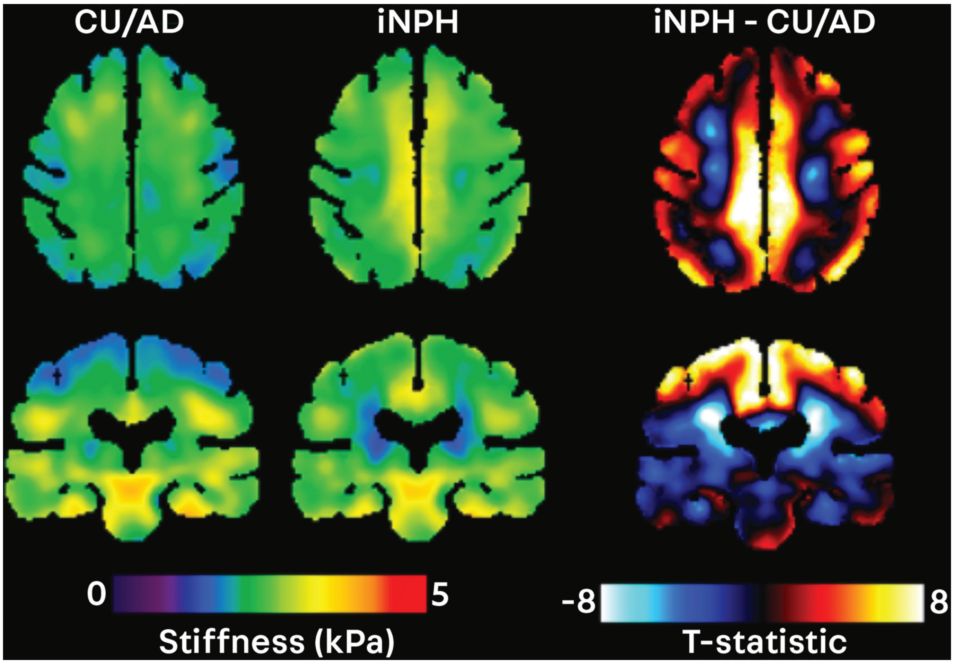

FIGURE 9-9

Pattern of brain stiffness in normal pressure hydrocephalus (NPH). ***Left column***, **Representative axial and coronal slices from stiffness maps for a group of cognitively unimpaired (CU) controls and patients with Alzheimer disease (AD).** ***Middle column***, **Mean stiffness maps in patients with idiopathic NPH (iNPH).** ***Right column***, **Maps of the T-statistic of the voxelwise stiffness difference of the idiopathic NPH group relative to the CU/AD group. The stiffness maps show the pattern of stiffening at the vertex (*red-yellow*) and periventricular softening (*blue-aqua*) that is characteristic of NPH.**

NUCLEAR MEDICINE STUDIES

Nuclear medicine imaging studies allow evaluation of brain function, as opposed to the predominantly structural information obtained with MRI. These techniques have patterns specific for idiopathic NPH, which are reviewed below, but they can also assess for conditions that mimic or confound the clinical presentation of idiopathic NPH.

Single-Photon Emission CT

Single-photon emission CT (SPECT) measures regional changes in cerebral blood flow. Regional cerebral blood flow patterns on SPECT typically show changes in the brain regions reflected in the DESH pattern. The cerebral apparent hyperperfusion sign is characterized by hypoperfusion in the frontal lobes and around the sylvian fissures and relative hyperperfusion in the high convexities (compared with SPECT of healthy controls).[96] The relative hyperperfusion is hypothesized to be related to increased gray matter volume in the convexities that results from upward displacement of the brain. Another study tried to replicate the cerebral apparent hyperperfusion sign but found an absolute hypoperfusion in the high convexities and suggested that the hyperperfusion could occur early in idiopathic NPH and evolve into hypoperfusion the longer the disease is present.[97] The cerebral blood flow pattern on SPECT is not able to predict shunt responsiveness.[16,98,99]

Dopamine Transporter Scan

Dopamine transporter scans can detect dopaminergic neuron dysfunction in the striatum. They can show symmetric decreased uptake in the caudates of

TABLE 9-1 Radiographic Predictors of Shunt Responsiveness in Patients With Normal Pressure Hydrocephalus

Modality and finding[a]	Comment
MRI or CT disproportionately enlarged subarachnoid space hydrocephalus (DESH) pattern	Presence of high-convexity tight sulci and enlarged sylvian fissures predicts positive shunt response
MRI or CT posterior callosal angle	<63° predicts positive shunt response
MRI extent of white matter hyperintensities	More extensive white matter hyperintensities are negatively associated with clinical improvement after shunt placement
MRI diffusion tensor imaging (DTI)	Advanced DTI techniques assess normal pressure hydrocephalus severity, distinguishing idiopathic normal pressure hydrocephalus, *ex vacuo* ventriculomegaly, and healthy controls, as well as separating patients who respond to shunt placement from those who do not
MR elastography (MRE)	Pattern of brain stiffening at the vertex and periventricular softening predicts positive shunt response

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[a] The absence of these features does not necessarily mean the patient will not benefit from permanent CSF diversion surgery.

individuals with idiopathic NPH, which is distinct from the uptake pattern seen in patients with Parkinson disease.[100] One study found that the striatal binding ratio (SBR), a semiquantitative measure of dopamine transporter activity in the basal ganglia, could differentiate idiopathic NPH from mimics, including cases of progressive supranuclear palsy, dementia with Lewy bodies, idiopathic Parkinson disease, and others.[101] In another study of idiopathic NPH patients with shuffling gait, hesitation or freezing, and en bloc turning, caudate striatal binding ratio correlated with Movement Disorder Society (MDS)–Unified Parkinson's Disease Rating Scale (UPDRS) and idiopathic NPH rating scale scores, with all measures showing improvement after shunting.[102] To date, no studies have formally evaluated the ability of dopamine transporter scans to predict shunt responsiveness in idiopathic NPH.

Fludeoxyglucose Positron Emission Tomography

Imaging with FDG-PET measures glucose metabolism throughout the brain. FDG-PET is commonly used in the evaluation of patients with dementia to look for characteristic patterns of hypometabolism associated with several neurodegenerative diseases.[103] In the absence of a coexistent neurodegenerative disease, patients with NPH have preserved cortical metabolism, although they may have hypometabolism of the caudate and putamen.[104] Also, artifactual hypometabolism commonly occurs in association with enlarged CSF spaces (eg, sylvian fissures and focally enlarged sulci) secondary to partial volume effects (FIGURE 9-8).

MR ELASTOGRAPHY

MR elastography is a technique for quantitative and noninvasive evaluation of mechanical properties of tissues. In this method, low-amplitude shear waves are generated in the tissue by applying external acoustic vibrations through a pillow-like device in the head coil. MR images show how the waves propagate in the tissue, and a complex inversion is performed to determine quantitative, voxelwise measures of tissue stiffness.[105] Early studies of brain stiffness in patients with NPH showed conflicting results, some indicating increased brain stiffness[106-108] in the parietal and occipital lobes and others showing globally decreased brain stiffness in patients with NPH compared with controls.[109,110] Differences were likely, in part, related to the use of global versus regional measurements, as subsequent work analyzing patterns of brain stiffness showed that patients with NPH have a unique pattern of stiffening at the vertex and softening of the periventricular white matter that is different from age-matched controls and patients with Alzheimer disease (FIGURE 9-9).[111] The regions of increased stiffness at the vertex correspond with regions of effaced sulci in patients with morphologic features of DESH.

Limited data exist on changes in brain mechanical properties after shunt placement; Freimann and colleagues[110] showed that microstructural tissue organization improved to near normal values after treatment. There were no changes in stiffness; however, the vertex, the region of greatest stiffness in the setting of NPH, was not included in their analyses. Clinical improvement after shunt placement is associated with increased stiffness in the deep gray matter and white matter and specific regional features derived from pattern analysis.[106,112,113]

KEY POINTS

- **Single-photon emission CT (SPECT) studies of patients with NPH have demonstrated apparent hyperperfusion at the high convexities, thought to be related to increased gray matter volume in high-convexity tight sulci, and hypoperfusion about the enlarged sylvian fissures, which may be related to partial volume effects.**

- **Dopamine transporter scans may show reduced radiotracer uptake in the caudate in patients with NPH, in a pattern that is unique from patients with Parkinson disease, suggesting utility in differential diagnosis and evaluation for copathology.**

- **Characteristically, there is no cortical hypometabolism associated with structural features of DESH, and fludeoxyglucose positron emission tomography (FDG-PET) is useful to evaluate for alternative or coexisting neurodegenerative processes that account for a patient's symptomatology.**

- **FDG-PET may show hypometabolism in the caudate and putamen of patients with NPH.**

- **MR elastography shows a unique pattern of stiffening at the vertex and softening of the periventricular white matter in patients with NPH.**

Of all the imaging modalities currently in clinical or research use for evaluating NPH, relatively few have been shown to predict shunt responsiveness. These are summarized in **TABLE 9-1**.

CONCLUSION

Methods used to evaluate for imaging features of NPH have evolved over the past few decades, moving from radionuclide cisternography to MRI as the primary modality for identifying supportive radiographic features. Several structural features and subtypes of NPH have been described, most notably the DESH pattern of idiopathic NPH and LOVA and PaVM patterns of congenital hydrocephalus. Advanced imaging techniques have been applied, primarily in the research setting, to study the movement of CSF. PET imaging has also shown characteristic patterns in the setting of NPH, although it is most useful to evaluate for alternative or coexistent pathology rather than demonstrate supportive features of NPH, per se. In the future, it would be valuable to better understand which imaging features best correlate with clinical symptomatology and may be used to predict outcomes after CSF diversion surgery.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Management of Normal Pressure Hydrocephalus

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ABSTRACT

OBJECTIVE: This article reviews the preoperative considerations, postoperative complications, and ongoing management of shunts for normal pressure hydrocephalus.

LATEST DEVELOPMENTS: The radiographic pattern of disproportionately enlarged subarachnoid space hydrocephalus (DESH) predicts a positive response to permanent CSF diversion. MRI-safe programmable shunt valves allow for fluid drainage adjustment based on patients' symptoms and radiographic images. Endoscopic third ventriculostomy is a viable alternative to shunting for patients with normal pressure hydrocephalus due to aqueductal stenosis.

ESSENTIAL POINTS: Approximately 75% of patients with normal pressure hydrocephalus improve after shunt surgery regardless of shunt type or location. Clinical benefit and complication rates are similar for frontal and parietal ventricular catheter approaches. Acetazolamide is not an effective treatment for normal pressure hydrocephalus.

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INTRODUCTION

Normal pressure hydrocephalus (NPH) is a pathologic condition whereby excess CSF is retained in and around the brain despite normal intracranial pressure.[1] This condition can be primary (idiopathic) when there is no identifiable cause or secondary (symptomatic) when there is an identifiable cause such as trauma, infection, or hemorrhage.[1] Both primary and secondary NPH are treated surgically, but the approach may vary by indication, patient factors, and surgeon and institution preference. For more on the clinical presentation and diagnosis of this condition, refer to the article "Clinical Features and Diagnosis of Normal Pressure Hydrocephalus" by Abhay R. Moghekar, MBBS,[2] in this issue of *Continuum*.

NPH typically occurs in older patients, and surgical decision-making for NPH must account for the comorbidities that come with increasing age.[3,4] The average age of onset is approximately 70 years, with equal prevalence in men and women.[3,4] The estimated incidence is 0.2 to 5.5 per 100,000 person-years, with a prevalence of 0.003% in people younger than 65 years old and 0.2% to 2.9% in people 65 years old and older.[3,4] Permanent CSF diversion, which includes ventriculoperitoneal shunting, lumboperitoneal shunting, or endoscopic third ventriculostomy, is the current standard treatment of NPH.[5-7] The clinical and radiographic features that predict which patients will benefit from permanent CSF diversion are discussed elsewhere in this issue. For more information, see the article “Radiographic Evaluation of Normal Pressure Hydrocephalus” by Petrice Cogswell, MD, PhD, and Aaron Switzer, MD, MSc,[8] in this issue of *Continuum*. This article describes the approach for patients who have already been identified as likely to be shunt responsive and discusses other factors that should be considered preoperatively, intraoperatively, and postoperatively. This article reviews the various surgical approaches, surgical and shunt valve management strategies, outcomes, and complications associated with shunting in patients with NPH.

The only definitive treatment for NPH is CSF diversion or shunting. Despite many patients improving with shunt placement, there is significant reluctance among many neurologists and surgeons to offer shunt surgery because of the relatively high number of patients who do not experience significant improvement, the lack of improvement durability in some patients who have initially positive responses, and the morbidity associated with the procedure in older age groups.[1,5-7,9,10] Nevertheless, CSF diversion remains an important procedure for improving the quality of life for appropriately selected patients with NPH.[1,5-7,9,10] Although acetazolamide reduces CSF production and might be predicted to have a similar effect to shunt surgery of decreasing the amount of CSF in the cranial vault, this medication is not effective for NPH and should not be offered to patients for this indication.

SURGICAL APPROACHES

Permanent CSF diversion can be accomplished with ventricular or lumbar shunts, which can feature fixed or programmable valves with drainage catheters terminating in a variety of body locations.

Ventricular Shunts

Extracranial ventricular shunts are the most common surgical treatment for patients with NPH.[1,5-7,9,10] Options include ventriculoperitoneal, ventriculoatrial, and ventriculopleural shunts, among others.[1,5-7,9,10] In these procedures, a ventricular catheter is inserted into the ventricle and attached to a valve that is then connected to a longer catheter that runs in the subcutaneous tissue to its terminal location. The ventricular catheter is typically placed into the frontal horn of the lateral ventricle through a frontal (Kocher point) or parietal or occipital (the Frazier, Keen, and Dandy points) burr hole.[11-13] The advantages of the frontal approach are that it is the shortest distance to the lateral ventricle, has minimal reliance on surgical navigation, and has minimal interaction with the choroid plexus to minimize potential catheter obstruction.[11-13] The disadvantages of the frontal approach include that it is difficult to communicate the bilateral lateral ventricles through one pass and it requires a separate parietal incision in the suboccipital region to allow the distal catheter to be directed to the terminal position.[11-13] The advantages of the parietal approach are that it allows communication of the bilateral lateral ventricles through one pass, it requires traversing less brain parenchyma to access the atrium of the lateral ventricle, it allows for the longest length of catheter to be positioned inside the ventricles for optimal drainage, a separate subcutaneous incision is not needed to direct the catheter to the terminal position, and the valve can sit behind the ear for better cosmesis.[11-13] The disadvantages of the parietal approach are that it has the smallest margin for error and therefore typically requires stereotactic navigation, is less familiar to most surgeons, and comes close to the choroid plexus and therefore has more potential risk of obstruction.[11–13] In a retrospective review of patients with NPH, there was no difference in clinical outcomes for ventricular catheters with a frontal versus parietal approach, including no significant differences in rates of complications or need for revision surgery.[13]

The authors prefer a parietal approach on the nondominant side largely because it avoids a second scalp incision as a potential entry for infection. A longer length of catheter is inserted, aiming for the contralateral frontal horn to allow communication of the bilateral lateral ventricles in cases of asymmetric ventricles and to avoid the choroid plexus and associated risk of obstruction. This approach is done under navigation guidance to minimize the risk of shunt malposition. For ventriculoperitoneal shunts, the authors usually operate with a general surgeon for laparoscopic placement of the peritoneal catheter. This allows ideal localization of the catheter in the right upper quadrant, around the liver away from the omentum and bowels, to minimize the risk of obstruction. The valve is placed away from the incision line to minimize dehiscence, which is especially important in patients who are frail, subject to falls, and older. This is done by pulling the catheter from the peritoneal end to allow the valve to slide underneath the skin incision. After the procedure, the patient is typically observed overnight as an inpatient. A head CT is done on postoperative day 1 to confirm the location of the proximal catheter, establish baseline ventricular caliber for future comparison, and rule out early overdrainage, subdural fluid collections, and hemorrhage.

Lumbar Subarachnoid Shunts

Unlike a ventricular shunt, a lumbar shunt involves placing the proximal catheter into the intrathecal space in the lumbar spine.[14] This is typically done at the L4-L5 interspace through a superficial cutdown to the paravertebral fascia. A Touhy needle is then placed into the subarachnoid space, and the proximal catheter is tunneled into the subarachnoid space before the needle is withdrawn.[14] This is similar to a lumbar drain. The catheter is then connected to a valve connected to a distal catheter that runs to the peritoneal space.[14] The advantages of a lumboperitoneal shunt are that it avoids traversing brain parenchyma and thus eliminates the risk of cerebral hemorrhage, has a low risk of catheter malposition as it does not rely on ventricular location, and has a lower risk of seizures.[14] Complication rates for lumboperitoneal shunts are higher; the risk of overdrainage is greater because of the column effect of gravity on CSF in the spine, and it is more challenging to adjust valve settings because of the increased amount of soft tissue in the lumbar region as compared with the scalp.[14] Although this approach is commonly used for patients with idiopathic intracranial hypertension where the ventricular caliber is small, it is being increasingly used at some centers for patients with NPH.[14]

Position of the Distal Catheter

The terminal position of the shunt catheter can be the peritoneum, jugular vein, right atrium, or pleural space.[1,5-7,9,10] Other spaces have been used for the terminal catheter far less frequently and include the gallbladder and urinary bladder.[1,5-7,9,10] For peritoneal catheters, the distal catheter is placed in the peritoneum through a transabdominal incision.[15,16] This is the preferred site for distal catheter placement because the large cavity size minimizes the risk of distal obstruction and fluid accumulation and relatively constant pressures in the peritoneal cavity facilitate consistent shunt drainage.[15,16] Retrospective series have shown the utility of laparoscopic placement of the catheter in the peritoneal cavity, as this allows better positioning of the catheter under direct visualization, facilitates lysis of adhesions if present, and is less invasive than open laparotomy (**FIGURE 10-1**).[15,16]

In cases in which the peritoneal cavity is not ideal for the placement of the distal catheter, such as patients with abdominal pathologies, significant history of abdominal procedures, adhesions, or peritonitis, the distal catheter can also be placed through the jugular or facial vein to the superior vena cava and right atrium.[17] This can be done via a cutdown or, more commonly, percutaneously with ultrasound guidance similar to central line placement.[17] The advantages of atrial placement of the distal catheter are that it can be done percutaneously, the distance the distal catheter has to traverse is relatively short, and the pressure within the venous system is relatively constant and therefore subject to less siphoning effects.[17] Conversely, the atrial location is more prone to clot formation and distal catheter obstruction, sometimes antiplatelet or anticoagulation therapy is needed, and the shunt tip can cause arrhythmia when close to the sinoatrial node.[17] To minimize these risks, the shunt tip is targeted to the junction of the superior vena cava and right atrium. In cases where the patient has poor vascular anatomy, a history of thrombosis at the venous site, or sepsis, another possible site is the pleural space.[18] Pleural catheter placement is similar to a chest tube, above the intercostal space through a skin incision.[18] Complications associated with this location are the risk of overdrainage because of the siphoning effect with inspiration that creates negative pressure and the risk of pleural effusion or hydrothorax.[18]

Adjustable Versus Fixed Pressure Valves

CSF shunts work based on a pressure differential where the CSF drains from the ventricular or subarachnoid compartment into the peritoneum or other distal compartment when the pressure is higher in the proximal compared with the distal compartment. The shunt system has a valve between the proximal (ventricular or subarachnoid) catheter and distal (peritoneal, atrial, or pleural) catheter. The valve can be either a fixed pressure valve with a preset setting that cannot be changed or an adjustable valve, whereby the setting can be adjusted with an external magnetic device.[6] Although the outcomes and complications between the different valve types are similar, the use of adjustable valves has a slightly lower risk of overdrainage and need for revision surgery.[6] Fixed pressure valves have the advantage of not having unexpected shunt setting changes that can lead to overdrainage or underdrainage. Also, patients with fixed pressure valves can undergo MRI without checking shunt settings.[6] If the patient needs more or less drainage based on symptoms or imaging however, the shunt valve must be replaced during another surgery.[6] For these reasons, adjustable valves, many of which are MRI-safe, are being used more often than fixed pressure valves for patients with NPH.[6]

Endoscopic Third Ventriculostomy

Endoscopic third ventriculostomy involves placing an endoscope into the lateral ventricle and navigating it through the foramen of Monro to create a hole in the

KEY POINTS

- **Normal pressure hydrocephalus (NPH) occurs in older patients, with an average age of onset of 70 years and equal prevalence in men and women.**
- **The only definitive treatment for NPH is CSF diversion or shunting.**
- **Acetazolamide is not an effective treatment for NPH.**
- **There is no significant difference in clinical benefit, complication rate, or the need for revision surgery for ventricular catheters with a frontal versus parietal approach in patients with NPH.**
- **The peritoneal cavity is the most common site for distal catheter placement because the large cavity size minimizes the risk of distal obstruction and relatively constant intracavitary pressures facilitate consistent shunt drainage.**
- **Ventriculoperitoneal shunts drain when the pressure is higher in the proximal (ventricular) as compared with the distal (peritoneal) compartment.**
- **Fixed and adjustable CSF shunt valves offer similar clinical benefits, with slightly lower rates of overdrainage and the need for revision surgery with adjustable valves.**
- **Endoscopic third ventriculostomy is reserved for patients with hydrocephalus due to obstruction of the aqueduct of Sylvius.**

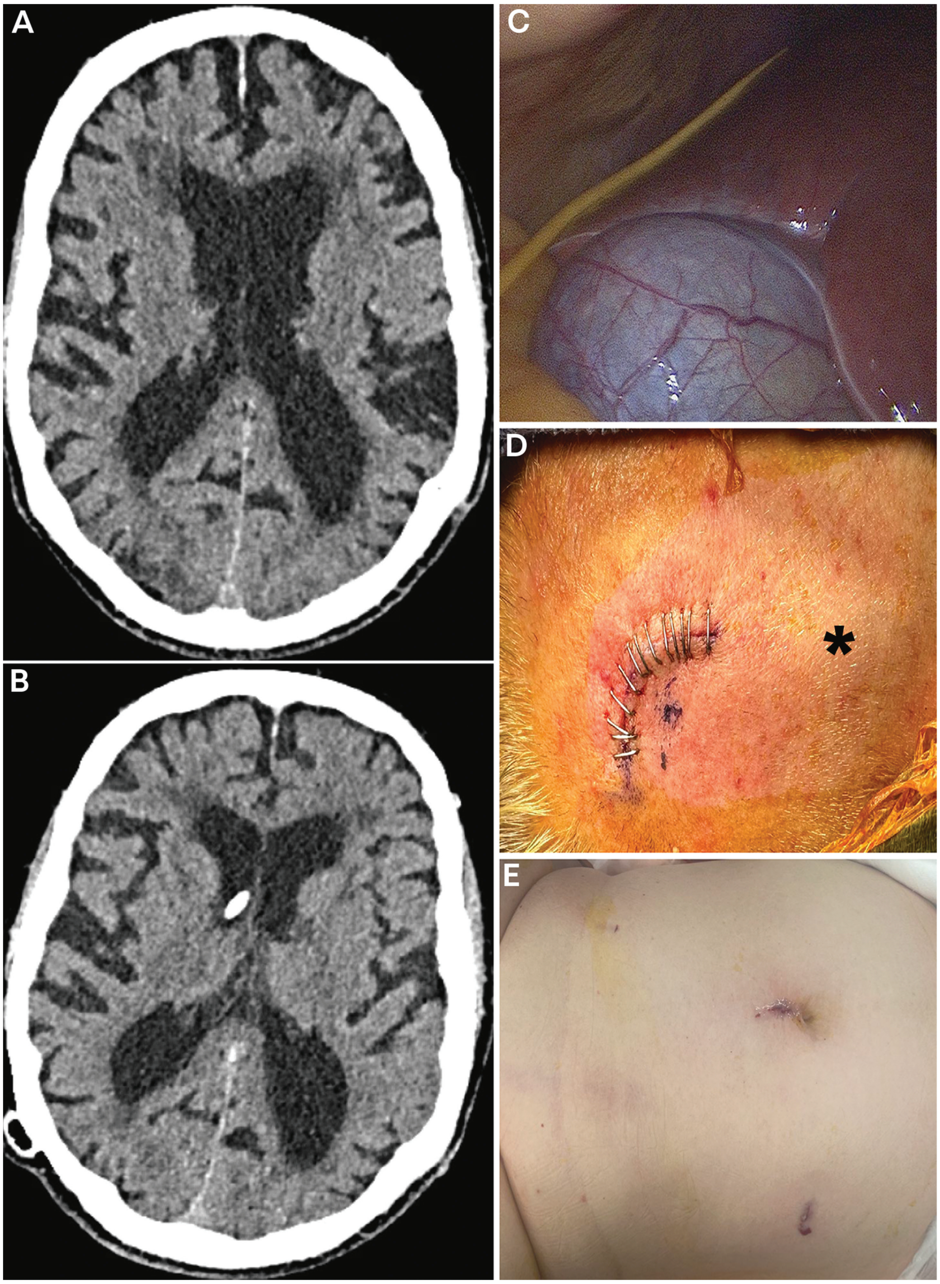

FIGURE 10-1

A patient with idiopathic normal pressure hydrocephalus. *A*, Preoperative noncontrast head CT shows ventriculomegaly and expanded sylvian fissures characteristic of the disproportionately enlarged subarachnoid space hydrocephalus (DESH) variant of idiopathic normal pressure hydrocephalus. *B*, Postoperative noncontrast head CT shows the placement of a right parietal ventricular catheter. *C*, Intraoperative laparoscopic image shows localization of the distal catheter over the liver, minimizing potential obstruction. *D*, *E*, Immediate postoperative images show the location of the incision relative to the programmable valve (*D*, *asterisk*) and abdominal incisions where laparoscopes were placed (*E*).

floor of the third ventricle between the infundibular recess anteriorly and the mamillary bodies posteriorly. This procedure is reserved for hydrocephalus due to obstruction at the aqueduct of Sylvius. It requires sufficient pressure to keep the hole open to allow sufficient fluid diversion over time.[19] The advantages of this approach are its minimally invasive nature and the avoidance of permanent indwelling hardware. Endoscopic third ventriculostomy has a higher failure rate than typical ventriculoperitoneal shunting for patients with NPH.[6,19] Endoscopic third ventriculostomy is not typically used for idiopathic NPH but may be considered for long-standing overt ventriculomegaly in adults and other cases of secondary NPH with aqueductal stenosis (**FIGURE 10-2**).[6,19]

SURGICAL PLANNING

The most important step of shunt surgery is diagnosis and indication.[20,21] Without an accurate diagnosis of NPH and a good indication for shunt placement, the placement of a shunt is unlikely to result in any significant benefit and can instead be associated with an increased risk of complications.[20,21] In a 2021 meta-analysis, the tests with the highest positive predictive value were intracranial pressure monitoring, lumbar drainage trial, intrathecal infusion, and high-volume lumbar tap test.[21] Because of the relative invasiveness of intracranial pressure monitors and lumbar drains, a high-volume spinal tap is typically performed, and if equivocal, a lumbar drain or intracranial pressure monitor may be pursued.[21] The most common radiographic signs associated with improved outcomes following shunt surgery in patients with NPH are the presence of disproportionately enlarged subarachnoid space hydrocephalus (DESH) with high-convexity tight sulci, elevated Evans index, and acute callosal angle; however, these radiographic signs are not universally associated with positive outcomes in different studies.[20] Patients with gait apraxia as the primary symptom are more likely to respond to shunting. Other features associated with

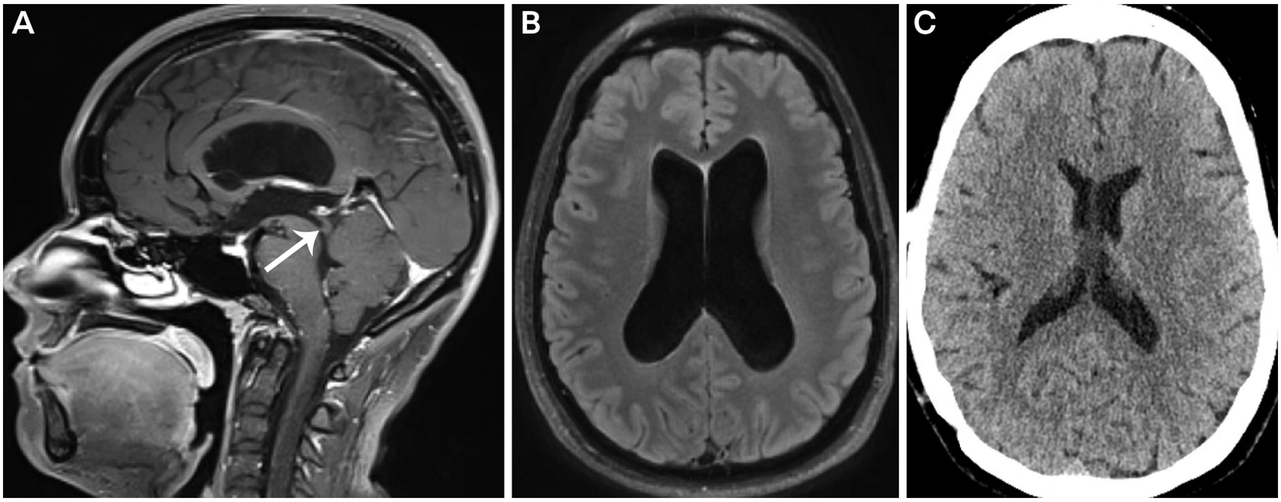

FIGURE 10-2

MRI of a patient with secondary normal pressure hydrocephalus from aqueductal stenosis. Preoperative sagittal T1-weighted with contrast (*A*) and axial fluid-attenuated inversion recovery (FLAIR) (*B*) MRI shows aqueductal stenosis (*A*, *arrow*) and enlargement of the lateral and third ventricles. Long-term postoperative axial noncontrast head CT (*C*) shows resolution of hydrocephalus after endoscopic third ventriculostomy.

improved outcomes include younger age, shorter duration of symptoms (less than 12 months), less severe symptoms based on the modified NPH scale score, and the absence of strokes.[21] When surgery is offered to treat NPH, it should be done sooner rather than later to maximize the time of improved quality of life.

SHUNT VALVE MANAGEMENT

The authors prefer using MRI-safe programmable valves. Despite the MRI compatibility, x-rays are still obtained before and after MRIs to confirm the shunt setting, and the shunt device is used at every clinic visit to confirm the shunt setting. A programmable valve allows the regulation of fluid drainage through the shunt system based on the patient's symptoms and radiographic images. The authors typically insert the valve at the setting just above that which correlates with the patient's opening pressure on preoperative lumbar puncture. This reduces the risk of overdrainage. The patient is seen 2 to 4 weeks postoperatively to check the incisions and assess the early response to the shunt. If the patient has not benefitted from the shunt, the setting is lowered by 1.0 to increase drainage; because the shunt valve setting represents pressure or resistance to flow, lower shunt settings allow more drainage. If the patient develops symptoms of overdrainage at any time, primarily headaches upon standing and with the Valsalva maneuver, a head CT or MRI is obtained and the shunt valve setting is increased by at least 1.0 to reduce drainage (CASE 10-1). The patient is typically seen at 2-month to 6-month intervals until the ideal shunt setting is determined. It is important to educate patients and their families that shunt surgery will not restore normal function, and it is more likely that it will improve their function in line with the improvement seen after the diagnostic high-volume lumbar tap.

SURGICAL COMPLICATIONS

The most common shunt surgery–related complications are subdural hematomas and hygromas from overshunting, intracranial hemorrhage, stroke, seizure, and infection.[1,6,7,13] Overdrainage can lead to the development of subdural hematomas from the rupture of bridging veins or to the accumulation of subdural hygromas.[1,6,7,13] This occurs in approximately 9% of patients regardless of shunt type, and 85% of hematomas regress spontaneously in cases in which an adjustable valve was placed and the setting can be adjusted to decrease CSF drainage.[6] Intracranial hemorrhage and stroke can occur with shunting from catheter placement or ischemia during surgery, with an incidence of around 2%.[6] There is a paucity of data regarding the incidence of seizures with shunt placement, but one study showed it occurring in 2% of patients undergoing ventriculoatrial shunting.[6] Seizures are most likely at the time of shunt placement, secondary to cortical irritation by direct contact with the ventricular catheter, or later in the setting of overdrainage.

Shunt infections can also occur, with an incidence of around 2% in most studies, with no significant difference between shunt types.[6] Perioperative mortality for patients with NPH shunts is less than 2%, with the majority due to hemorrhage and infection.[6]

Shunt failure can occur because of shunt malposition, catheter dislocation, obstruction, infection, and other reasons.[1,6,7,13] Shunt malposition can be minimized with the use of surgical navigation to guide catheter placement within

KEY POINTS

- The radiographic pattern of disproportionately enlarged subarachnoid space hydrocephalus (DESH) predicts but does not guarantee a positive response to shunt surgery in patients with idiopathic NPH.
- MRI-safe programmable shunt valves allow for CSF drainage adjustment based on patients' symptoms and radiographic images.
- Shunt surgery for NPH typically does not restore normal neurologic function.
- The most common surgery-related complications associated with shunting for NPH are subdural hematoma or hygroma from overdrainage, intracranial hemorrhage, stroke, seizure, and infection.
- CSF shunt revision is required in approximately 16% of patients treated for NPH.

the ventricles. Catheter dislocation can occur because of detachment from the valve or sheering because of trauma. Catheter obstruction can occur in both the proximal and distal catheters from various sources including choroid plexus, debris, and hemorrhage. Shunt infection can occur at the surgical site (eg, wound dehiscence) or as a consequence of infections such as sepsis or meningitis.[1,6,7,13] Among all patients shunted for NPH, the incidence of shunt revision is around 16% from all causes, with around 10% of these the result of shunt failure.[1,6,7,13] In cases of shunt failure not caused by infection and after a prolonged period since shunt placement, it may be appropriate to repeat a high-volume lumbar tap or lumbar drain trial to ensure that the patient's neurologic impairments are still responsive to CSF diversion before revising the shunt. In cases of shunt infection, the entire shunt system should be removed, with replacement only after the infection has been adequately treated.

CASE 10-1

A 75-year-old man was diagnosed with idiopathic normal pressure hydrocephalus based on 2 years of progressive gait freezing, urinary incontinence, and mild cognitive impairment. Brain MRI showed disproportionately enlarged subarachnoid space hydrocephalus (DESH). A ventriculoperitoneal shunt was placed via a right parietal approach with a valve setting of 5.0. At the first postoperative visit 1 month later, he and his family reported symptom improvement, including faster walking with less freezing, resolution of incontinence, and clearer thinking. However, he described new headaches consistently triggered by standing or coughing. Brain MRI showed thin subdural fluid collections and diffuse dural enhancement. He had no history of head trauma and he was not anticoagulated. Because of suspected shunt overdrainage, the valve setting was adjusted to 6.0. One month later, his headaches had resolved, and he was still enjoying the improvements in gait, bladder control, and cognitive function reported at the earlier visit. Brain MRI showed resolution of the subdural fluid collections and dural enhancement. Ventricular caliber did not change.

COMMENT

This patient had clinical and radiographic features of normal pressure hydrocephalus, and improvement after ventriculoperitoneal shunt surgery further supported the diagnosis. Shunt overdrainage is a risk of any type of shunt via any approach and typically causes headaches that are worse with upright posture and Valsalva maneuvers. Radiographically, shunt overdrainage can mimic spontaneous intracranial hypotension, more often with dural enhancement and subdural fluid collections and less often with brain sag. Dural enhancement without subdural hematomas or symptoms does not necessarily require intervention, but symptomatic overdrainage should be addressed by reducing CSF drainage via increasing the valve setting, as a higher valve setting requires higher intracranial pressure for CSF drainage. For fixed valve systems, overdrainage can be addressed only by clamping the shunt or replacing the valve. The optimal shunt setting is the highest setting that still allows for patient improvement.

CSF DIVERSION SURGERY OUTCOMES

Surgical outcomes for NPH are far from uniform. In a 2019 meta-analysis, Giordan and colleagues[6] found that approximately 75% of patients improved following shunt placement. The proportion of patients who reported improvement decreased over time. They found that 78% of patients reported improvement for follow-up times less than 12 months, declining to 73% for patients followed 12 to 36 months, and 71% after 36 months.[6] There was no significant difference in outcomes based on shunt type (ventriculoperitoneal versus ventriculoatrial versus lumboperitoneal).[6] Gait improvement was reported in 75% of patients.[6] Cognitive improvement ranged from 55% to 63%.[5] Urinary incontinence improved in 54% of patients.[6] These data reinforce the need to shunt early once a diagnosis of NPH is established as the durability of improvement decreases over time.

CONCLUSION

The standard treatment of NPH is permanent CSF diversion, which can be accomplished with ventriculoperitoneal, ventriculoatrial, ventriculopleural, or lumboperitoneal shunts. Each shunt type has advantages and disadvantages, but surgical outcomes and complications are similar among them. Endoscopic third ventriculostomy is a viable alternative in patients with NPH due to aqueductal stenosis. CSF diversion can improve quality of life for appropriately selected patients with NPH but may lose some effect over time.

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REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Childhood-onset Hydrocephalus

By Shenandoah Robinson, MD, FAANS, FAAP, FACS

ABSTRACT

OBJECTIVE: This article highlights important concepts of caring for patients with childhood-onset hydrocephalus across the lifespan, emphasizing recent advances and current areas of controversy.

LATEST DEVELOPMENTS: There are numerous causes of symptomatic hydrocephalus in neonates, infants, and children, and each etiology predicts the typical clinical course across the lifespan. Because the major cellular components essential for CSF dynamics develop predominantly during the third trimester and first 6 months after term birth, directly overlapping with the onset of many types of fetal, neonatal, and infantile hydrocephalus, the timing of onset impacts lifelong management. The treatment of childhood-onset hydrocephalus varies dramatically worldwide due to the differing etiologies and access to neurosurgical interventions. The surgical options for CSF diversion have advanced over the past decade, with a better appreciation of which techniques are more successful for the various types of childhood-onset hydrocephalus. These advances include using temporary shunt devices to delay permanent CSF diversion and endoscopic third ventriculostomy, at times with choroid plexus cauterization.

ESSENTIAL POINTS: Etiology and age of onset impact the lifelong management of individuals living with childhood-onset hydrocephalus, with a rapid pace of evidence-based changes in clinical practice.

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INTRODUCTION

Childhood-onset hydrocephalus encompasses a wide range of disorders with varying clinical implications. Correct terminology can facilitate communication among providers and families. After describing terminology, the development of CSF dynamics, and the etiology of childhood-onset hydrocephalus, this article outlines methods of CSF diversion, lifelong management, and comorbidities. The differences between childhood-onset hydrocephalus and adult-onset hydrocephalus are highlighted.

TERMINOLOGY

Ventriculomegaly describes enlarged cerebral ventricles. Ventriculomegaly as a normal anatomic variant is usually a diagnosis of exclusion. Asymmetric ventricular enlargement is also a common anatomic variant and in isolation does not require further evaluation. Ventriculomegaly can also reflect a coexisting abnormality in parenchymal brain development when accompanied by atypical neurodevelopment, such as intellectual delay or autism spectrum disorder. *Hydrocephalus ex vacuo* describes enlarged ventricles in the setting of deficient parenchymal development accompanied by enlarged subarachnoid spaces, including the sylvian fissures. Hydrocephalus ex vacuo is typically found in the setting of a normal or small cranial size. By contrast, *symptomatic hydrocephalus* refers to altered CSF dynamics in the setting of elevated intracranial pressure (ICP). Usually, but not always, the ventricles enlarge with elevated ICP in childhood-onset hydrocephalus. *Transient hydrocephalus* refers to patients who have hydrocephalus at one point that requires surgical treatment but later no longer needs permanent CSF diversion. This scenario can occur after trauma, infection, or tumor in childhood, or in a subset of preterm infants who require a temporary shunt but not permanent CSF diversion.

In general, using the term *ventriculomegaly* to describe enlarged ventricles present on imaging, while reserving the term *hydrocephalus* for impaired CSF dynamics that may require intervention, reduces confusion among providers. Hydrocephalus implies an ongoing need for potential clinical management, whereas a chronic diagnosis of ventriculomegaly implies that CSF dynamics are functioning well in the setting of large ventricles (**FIGURE 11-1**). For example, an older child or adult with ventriculomegaly from spina bifida aperta (open spinal dysraphism, as opposed to spina bifida occulta) who had spontaneous development of adequate CSF dynamics as an infant and has not required

KEY POINTS

- ***Symptomatic hydrocephalus*** **generally refers to altered CSF dynamics in the setting of elevated intracranial pressure.** ***Transient hydrocephalus*** **refers to when a patient who had hydrocephalus at one point that required surgical treatment now no longer needs permanent CSF diversion.**

- **Using the term** ***ventriculomegaly*** **to describe enlarged ventricles present on imaging, while reserving the term** ***hydrocephalus*** **for impaired CSF dynamics that may require intervention, reduces confusion among providers.**

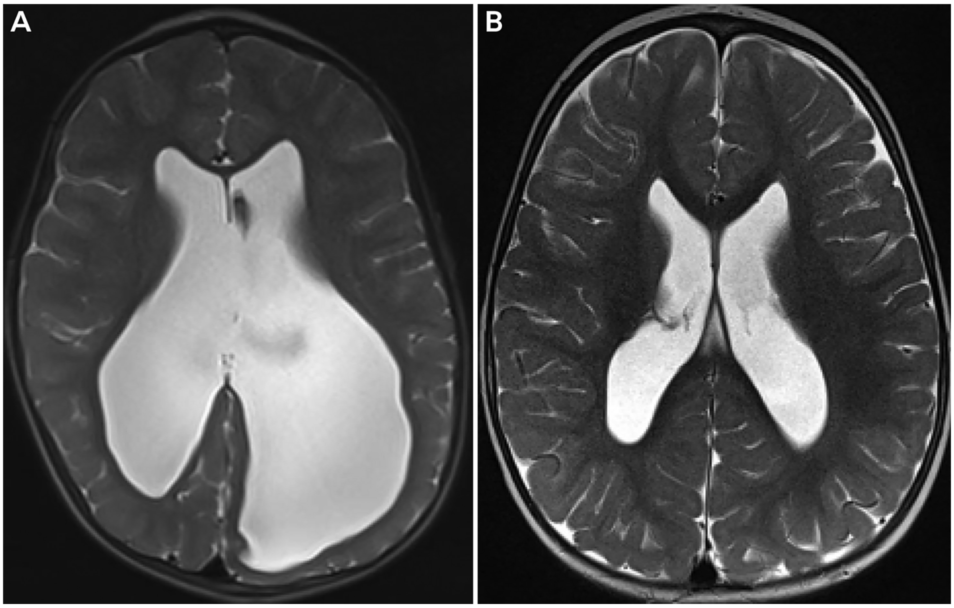

FIGURE 11-1
Imaging of a patient with cerebral ventriculomegaly. Children and adults with pediatric-onset disorders may have asymptomatic ventriculomegaly. *A*, Axial T2-weighted MRI from a 15-year-old person born very preterm. They performed better than their peers academically and had mild cerebral palsy, despite the significant ventriculomegaly. *B*, Axial MRI from an asymptomatic 35-year-old person with congenital ventriculomegaly associated with spina bifida aperta.

surgical intervention during childhood is best described as someone with ventriculomegaly rather than hydrocephalus.

Before closure of the cranial sutures, serial examinations of the fontanel, sagittal suture splay, and head circumference can provide a surrogate for elevated ICP. The progression along the head circumference curve is more informative than the exact value. Head circumference charts are population specific, and familial head circumference measurements often provide reassuring context. Most widely used head circumference charts in the United States were generated from children with a Western European heritage and may not be accurate for children with different backgrounds. Infants born before 37 weeks of gestation should be evaluated with preterm head circumference charts. Specific charts for those with achondroplasia are also available.[1] The timing of fontanel closure can also vary and early or late closure of the fontanel in isolation is rarely a cause for concern.

Macrocephaly in neonates and infants can be a normal variant. A typical neurodevelopmental trajectory accompanied by a lack of clinical symptoms and signs of elevated ICP provides reassurance, especially in the setting of familial macrocephaly. Benign enlargement of subarachnoid spaces is a common anatomic variant found with macrocephaly in otherwise asymptomatic and typically developing infants or toddlers. Benign enlargement of subarachnoid spaces is often an incidental diagnosis found on imaging studies, such as for mild head injury. Once the diagnosis of benign enlargement of subarachnoid spaces is made, the child usually does not require follow-up or serial imaging. An infant with atypical development and macrocephaly may benefit from further evaluation by a developmental pediatrician or pediatric neurologist, depending on local referral patterns. A persistent rapid increase in head circumference that crosses percentiles, is confirmed on multiple measurements, and is accompanied by symptoms or signs of elevated ICP warrants further evaluation, with the urgency determined by the clinical scenario. The differential diagnosis in this setting includes symptomatic hydrocephalus from delayed presentation of congenital or perinatal causes and acquired hydrocephalus from infection, trauma, or tumor. Another common cause of acquired macrocephaly is subdural collections from abusive head trauma. Note that head ultrasonography has limitations in visualizing extraaxial collections and posterior fossa abnormalities. If available, a rapid MRI scan that does not require sedation provides ideal screening images.

Microcephaly without clinical symptoms in the setting of typical development and with gradual progression of cranial growth below but parallel to the standard curve is reassuring. Multisuture craniosynostosis as a cause for microcephaly, such as cloverleaf skull syndrome, is rare and immediately obvious on clinical examination. Thus, for an infant with a lack of cranial growth with delayed development, referral to a pediatric neurologist or developmental pediatrician is often appropriate to facilitate appropriate evaluation.

DEVELOPMENT OF CSF DYNAMICS

Four components comprise healthy CSF dynamics: (1) secretion of CSF by the choroid plexus and parenchyma, (2) propulsion of CSF by ependymal motile cilia, (3) reabsorption of CSF by the glymphatic system, and (4) pulsatility.

Recent advances in neuroscience have transformed our understanding of CSF dynamics.

Choroid Plexus

The choroid plexus secretes trophic factors essential for brain health across the lifespan. For example, the choroid plexus secretes the transcription factor orthodenticle homeobox 2, which enters the parenchyma and facilitates the maintenance of perineuronal nets.[2,3] CSF secretion begins in utero and is active by the third trimester. After inflammatory injury, such as from infection or hemorrhage, the choroid plexus increases secretion of both CSF volume and substances such as proinflammatory cytokines.[4] CSF is also secreted by the parenchyma, although the specific mechanisms are less well understood. The timing and mechanisms of recovery of the choroid plexus and parenchymal secretion of CSF after injury are areas of active investigation.

Ependymal Motile Cilia

The ependyma that lines the ventricular system has motile cilia that propel CSF in a directed manner.[5] Ciliary beating propels CSF and regulates ventricular development.[6] For example, CSF in the lateral ventricle is directed toward the foramen of Monro. Ependymal motile cilia develop during the third trimester and through the first 6 months after birth.[7] Ependymal motile cilia are also vulnerable to inflammatory injury from infection, trauma, and hemorrhage.[8,9] After injury, ependymal cilia can regenerate over approximately 3 weeks in preclinical models.[10] Recent advances in genetic ciliopathies that affect ependymal cilia have shed light on the role of ependymal cilia in contributing to both hydrocephalus ex vacuo and symptomatic hydrocephalus.

Glymphatic System

Perhaps the most dramatic change in our understanding of CSF dynamics has been the reconceptualization of the reabsorption of CSF. Previous dogma suggested that CSF is reabsorbed through the arachnoid villi. However, several excellent studies over the past decade have shown that solutes and waste products from the brain parenchyma enter perivascular channels and are reabsorbed through lymphatic channels, primarily at the skull base.[11,12] Perivascular astrocytes help regulate the fluid flow from the perivascular spaces to the extracranial lymphatics, and thus the collective process has been referred to as the *glymphatic system*. This field is rapidly evolving and areas of controversy remain. Recent progress with quantifying glymphatic flow using tracers visualized with MRI in humans has greatly accelerated our understanding of how impaired glymphatic system flow can impact hydrocephalus and numerous other neurologic disorders, including dementia, chronic pain, and autoimmune and neuroinflammatory disorders. Glymphatic system flow is directly dependent on neuronal activity during sleep.[13] Interested readers are referred to the 2022 review by Carlstrom and colleagues[14] and the 2024 review by Beschorner and Nedergaard.[15] The development of the glymphatic system and its recovery after injury are also areas of active investigation.

Pulsatility

Pulsatility refers to the impact of the heartbeat and respiration on CSF flow. Although pulsatility is known to impact CSF flow, its role during development and impact on childhood-onset hydrocephalus are less well understood.

KEY POINTS

- **Most widely used head circumference charts in the United States were generated from children with a Western European heritage and may not be accurate for children with different backgrounds.**
- **Subdural collections from abusive head trauma are a common cause of acquired macrocephaly.**
- **Four components comprise healthy CSF dynamics: (1) secretion of CSF by the choroid plexus and parenchyma, (2) propulsion of CSF by ependymal motile cilia, (3) reabsorption of CSF by the glymphatic system, and (4) pulsatility.**

ETIOLOGY OF CHILDHOOD-ONSET HYDROCEPHALUS

The etiology of childhood-onset hydrocephalus has important diagnostic, management, and prognostic implications. Thus, hydrocephalus etiology should be sought and recorded as a critical part of the patient's history. Many children will have mixed or cumulative etiologies, such as the occurrence of infection in someone with hydrocephalus from spina bifida.

The terminology of early-onset hydrocephalus classification is evolving, largely due to the increased availability of genetic testing. The complexity of this terminology has also increased, and specific descriptions are likely the most helpful. In common usage, congenital hydrocephalus implies a genetic etiology without a specific known malformation, such as spina bifida aperta, Dandy-Walker malformation, or aqueductal stenosis. Congenital hydrocephalus from a genetic variation such as a ciliopathy can be considered primary hydrocephalus. Acquired hydrocephalus or secondary hydrocephalus from another insult can occur in utero, perinatally, or during childhood. For example, intraventricular hemorrhage can occur midgestation, in a preterm neonate, or in a term neonate, with each age of onset conveying a different etiology and prognosis. Another example is hydrocephalus with spina bifida aperta. The myelomeningocele could be secondary to maternal medication exposure near conception, and hydrocephalus could be due to the underlying maldevelopment, prenatal inflammation from CSF exposure to amniotic fluid, or perinatal meningitis. Acquired hydrocephalus during childhood can occur after trauma, tumor, epilepsy surgery, infection, or, rarely, unknown etiologies. It is not uncommon for a child to have mixed etiologies. Important details for a person with childhood-onset hydrocephalus include any CSF infection or failed endoscopic procedures (**CASE 11-1**).

Significant regional variation in the etiology of hydrocephalus exists across the United States. For example, preterm birth with intraventricular hemorrhage is much higher in southern US states.[16] Regional variations in referral and insurance coverage patterns add complexity. Marked variation in the clinical management of patients with childhood-onset hydrocephalus has been noted across neurosurgical centers.[17,18] Although the variation undoubtedly reflects training patterns and personal preferences, the regional differences in hydrocephalus etiology are likely a major driver in the variation in clinical practice. Encouraging people with hydrocephalus and their families to keep accurate records of their diagnosis and treatment can assist with management as they relocate and change care teams.

Global Differences in Etiology

Marked differences also exist in the etiology of childhood-onset hydrocephalus around the world.[19] Many regions do not have resources to support sick neonates, especially those born very preterm, nor access to pediatric neurosurgical care. Worldwide, postinfectious hydrocephalus is the most common etiology.[19] The incidence of infantile hydrocephalus is highest in Africa and Latin America, and lowest in the United States and Canada.[19] Because of the high cost and limited availability of neurosurgical care, there is a significant effort to develop nonsurgical treatment for some types of childhood-onset hydrocephalus. Greater access to folate fortification of food will hopefully reduce the global incidence of spina bifida and the often-associated hydrocephalus.

TREATMENT OF CHILDHOOD-ONSET HYDROCEPHALUS

This section reviews treatment options with specific considerations for childhood-onset hydrocephalus.

Nonsurgical Treatment

Currently, the options for nonsurgical prevention or treatment of hydrocephalus are limited. Efforts to reduce conditions associated with childhood-onset hydrocephalus in the United States have not yet had a substantial impact. For example, the US rate of preterm birth has remained stable despite attempts to reduce it.[20] Efforts are underway by neonatologists to reduce the incidence of intraventricular hemorrhage associated with extremely preterm birth. Prenatal fetoscopic closure of myelomeningocele may further reduce the proportion of infants with spina bifida aperta who require CSF diversion. Acetazolamide is used to reduce papilledema in selected patients, such as children with acquired hydrocephalus from a tumor. Acetazolamide rarely provides sustained relief of symptomatic hydrocephalus in children and is not recommended for preterm neonates with intraventricular hemorrhage.[21]

Temporary CSF Diversion

Surgeries to provide temporary CSF diversion include an external ventricular drain, ventricular access device, and ventriculosubgaleal shunt. For infants and children, an external ventricular drain can temporarily relieve obstructive hydrocephalus such as before tumor resection. Acquired hydrocephalus from infection or trauma may be transient, and an external ventricular drain can provide relief over 1 to 2 weeks while CSF dynamics recover. If dependence on the external ventricular drain cannot be weaned, the CSF will require permanent diversion.

Because of risks associated with external ventricular drains, they are rarely used in neonates, especially those born preterm. Temporary CSF diversion in preterm neonates is provided by ventricular access devices with serial removal of CSF or ventriculosubgaleal shunt where the CSF drains into a subgaleal pocket. The efficacy and complications of the two options are similar.[22] Approximately 25% of infants who undergo a temporary shunt will have spontaneous recovery of their CSF dynamics and not require long-term CSF diversion. The temporary shunt allows this subgroup of preterm infants to avoid the long-term consequences of a permanent shunt, including the need for long-term neurosurgical follow-up. Temporary shunts are often not removed even when they are no longer functional. Multiple studies have shown that older age at the time of permanent shunt insertion is associated with fewer shunt revisions over the patient's lifetime.[23,24]

Some older infants and children with transient hydrocephalus from infection, trauma, or epilepsy or tumor surgery may require CSF diversion for more than the few weeks provided by an external ventricular drain. In such circumstances, a permanent shunt is often inserted to mitigate the risks of prolonged external ventricular drain placement. Typically, a shunt is deemed no longer necessary after a period of inpatient testing with the externalized shunt turned off to ensure the patient's own CSF dynamics have sufficiently recovered. If the patient lives far from neurosurgical care, a catheter with an access reservoir may be left in place to allow emergent access via a tap if needed.

Infants with chronic subdural hygromas may require prolonged drainage to relieve elevated ICP. After a few months, the subdural collection resolves and

KEY POINTS

- **The etiology of childhood-onset hydrocephalus provides important information about associated risk factors and comorbidities.**

- **Wide variation exists in the geographic distribution of different etiologies of childhood-onset hydrocephalus and clinical management patterns. Providers and families may need to adapt to different practice patterns.**

- **Acetazolamide rarely provides sustained relief of symptomatic hydrocephalus in children and is not recommended for preterm neonates with intraventricular hemorrhage.**

- **Surgical options for temporary CSF diversion include an external ventricular drain, ventricular access device, and ventriculosubgaleal shunt. If dependence on the temporary device cannot be weaned, the CSF will require permanent diversion.**

rarely recurs. The subdural shunt is rarely removed due to the potential complications associated with the surgery. Unlike patients with permanent CSF diversion for hydrocephalus, patients with a subdural shunt rarely require long-term neurosurgical follow-up.

Permanent CSF Diversion

Permanent CSF diversion is currently provided by a ventricular shunt or endoscopic procedure. Regardless of the type of permanent CSF diversion, individuals with a history of treatment for persistent hydrocephalus are strongly encouraged to have ongoing follow-ups with an experienced care team. The structure of the care team varies across regions and institutions and often

CASE 11-1

A girl was born extremely preterm at 23 weeks postmenstrual age. Within a few days of birth, she had a large left periventricular hemorrhagic infarction (formerly known as a *grade IV intraventricular hemorrhage*). After several weeks, she developed marked ventriculomegaly and was referred to a neurosurgeon for treatment of posthemorrhagic hydrocephalus of prematurity. Brain MRI (FIGURE 11-2) showed a lack of sulci, typical of the preterm brain, and a bright signal in the cortical mantle secondary to impaired CSF dynamics. The clinical picture of enlarging head circumference that crossed percentiles when corrected for preterm birth, bulging fontanel, and splayed cranial sutures suggested elevated intracranial pressure. The infant underwent insertion of a temporary ventriculosubgaleal shunt. The fontanel became soft, and the cranial sutures were no longer splayed. After 6 weeks, the ventriculosubgaleal shunt was converted to a permanent shunt. On examination at age 3 years, the girl had a moderate right hemiparesis. She also had drug-resistant epilepsy, intellectual delay, cortical visual impairment, and typical comorbidities of extreme prematurity including chronic lung disease, gastric reflux, and gastrostomy tube dependence.

COMMENT

This case illustrates the management of patients with posthemorrhagic hydrocephalus of prematurity and the common comorbidities that occur in this setting. A ventriculosubgaleal shunt drains fluid from the ventricles into a subgaleal pocket in the scalp, allowing continual controlled decompression of the ventricles. Notably, even though intracranial pressure is relieved by a temporary ventriculosubgaleal shunt, it takes substantially longer for the cerebrum to reexpand (hence the need for a permanent shunt).

includes neurologists, neurosurgeons, and advanced practice providers. Children younger than 10 years old are often followed annually due to their growth and potential changes in intracranial dynamics. Once they have established care and depending on the circumstances, teenagers and adults are seen for routine follow-up less frequently. This change in the frequency of follow-up is ideally addressed with families as they prepare for the transition to adulthood. Baseline brain imaging provides an ideal reference point. Families who move and establish care at different institutions are encouraged to obtain a copy of prior imaging studies in addition to the written report. Routine follow-up with an ophthalmology team is also often advised as changes from baseline are most informative. Many individuals with hydrocephalus benefit from a

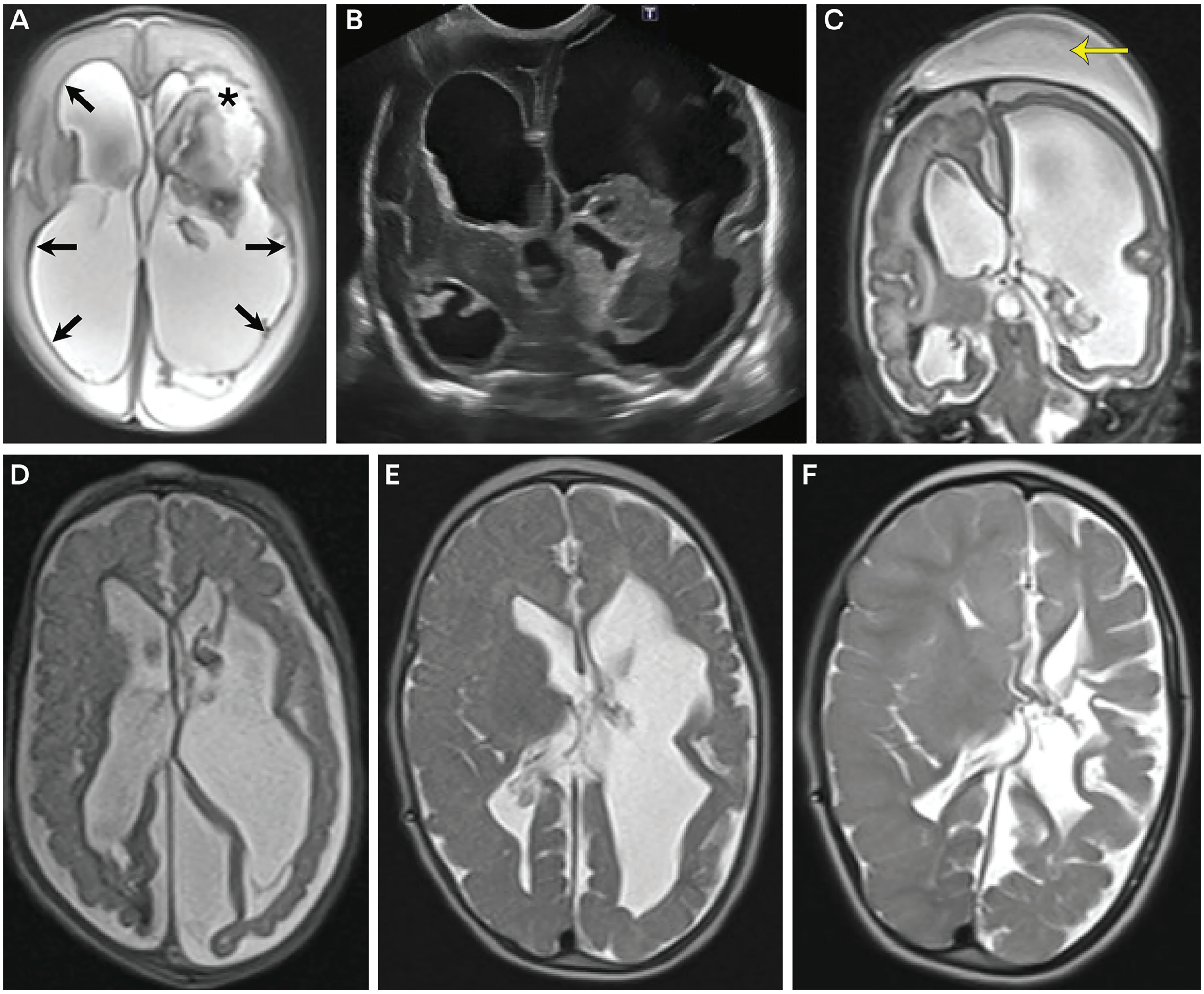

FIGURE 11-2
Imaging findings from the patient in **CASE 11-1**. *A*, At presentation, axial T2-weighted MRI at age 6 weeks shows left periventicular hemorrhagic infarction (*asterisk*) with marked venticulomegaly (*arrows*). *B*, Coronal head ultrasound image for comparison. *C*, A ventriculosubgaleal shunt has decompressed the ventricular system, with accumulation of CSF in the subgaleal pocket (*arrow*). *D*, *E*, *F*, Serial enlargement of the cortical mantle from ages a few months (*D*), 1 year (corrected) (*E*), and 3 years (*F*).

multidisciplinary care team across their lifespan to provide comprehensive care for sensorimotor impairments and associated comorbidities including epilepsy, chronic pain including headache, and cognitive and behavioral challenges.

PERMANENT VENTRICULAR SHUNTS. Permanent ventricular shunts are composed of a ventricular catheter, a valve to regulate flow, and a distal catheter. Ventricular catheters are commonly inserted from a frontal or occipital location. Neither insertion location is superior to the other. A *complex shunt* is a shunt with multiple functioning catheters or an atypical catheter location, such as a supratentorial or infratentorial catheter. Numerous types of valves exist, and no valve is superior to another type in multiple well-executed trials.[25] As mentioned above, populations of childhood-onset hydrocephalus vary regionally across the United States, and one valve design may be preferred over others for certain etiologies. Valves can be fixed at a specific opening pressure or programmable. Valves with fixed settings are not impacted by MRI. Some programmable valves are affected by the strong magnetic field used in MRI and need to be reprogrammed within a few hours after the MRI.

If an individual has a shunt, families are encouraged to keep track of the valve type and setting. Some valves are supplemented by an antisiphon device, which exists in several forms but generally works to prevent overdrainage induced by gravitational effects (siphoning) of fluid from a higher container (cranium) to a lower container (peritoneal cavity). Distal catheters are most commonly inserted in the peritoneal cavity. Less commonly, distal catheters are placed in the cardiac atrium or pleural space. Patient-specific factors may impact the choice of location for distal catheter placement. If the catheter placed in the peritoneal cavity fails at one point, the catheter can often be successfully reinserted in the peritoneal cavity after a few years. Typically, an adequate length of tubing is inserted initially and lengthening of distal catheters is rarely needed.

SHUNT COMPLICATIONS. Shunts are subject to malfunction and infection. Most shunt malfunctions in childhood-onset hydrocephalus are caused by occlusion of the ventricular catheter.[25,26] Valve malfunction and distal malfunction are much less common, unlike in adults. The presentation and severity of symptoms can vary tremendously across individuals. One person with exceedingly high ICP may report only mild headache, whereas another person with only mild elevation of the ICP may be incapacitated and lethargic. Common symptoms of shunt malfunction include intractable headache, emesis, and lethargy. Often an individual will have a distinct pattern of symptoms that distinguishes the symptoms and signs of shunt malfunction from other illnesses. Many individuals can identify the difference between a “shunt” headache and headaches from other etiologies. Symptoms from a proximal ventricular malfunction may be more acute and severe, whereas a lack of absorption of fluid in the peritoneal cavity may have a more protracted presentation. Shunts may function well for more than 20 years and then abruptly malfunction. Thus, a lack of a malfunction for many years should not lead to the assumption that the person is no longer shunt dependent (CASE 11-2). Valve malfunction can result from occlusion, which will manifest similarly to a catheter occlusion, or from being stuck open and causing overdrainage. Some programmable valves are susceptible to changes from magnets in the home environment. Distal malfunction can be caused by an intraabdominal process, including indolent or acute infection. Occasionally, no source is found and the catheter can be replaced in a different area of the peritoneal cavity.

In evaluating for possible shunt malfunction, imaging of the brain, shunt components, and abdomen is required but not always sufficient. If available, an MRI scan will provide details about the ventricular anatomy. CT scans can be used for older children and adults if clinical acuity warrants or if the type of valve is unknown. A shunt series of x-rays provides crucial details about the shunt components and serves as a roadmap at the time of surgery. Abdominal ultrasonography or CT scan helps to show CSF collections and other intraabdominal pathology. The evaluation typically begins with a shunt series of x-rays and either brain MRI or CT.

In patients with childhood-onset hydrocephalus, the goal of the shunt is to divert excess CSF and normalize the ICP. Some patients experience overdrainage of CSF, leading to headaches and other symptoms. For some patients, using an ICP monitor to confirm periods of low ICP can be very helpful. Various types of siphon control devices exist to mitigate these symptoms. Although siphon control devices are helpful in selected patients, they add another component that can malfunction.

Most shunt infections occur within 6 months of the last shunt manipulation, including a shunt tap. The widespread adoption of infection-reduction protocols has led to a decrease in the incidence of postoperative shunt infections. Infection-reduction protocols include preoperative baths, specific skin preparation practices, full scrubbing and double gloving by all scrubbed team members, timely preincision antibiotic administration, changing outer gloves after draping, limited touching of shunt hardware with gloves, antibiotic-impregnated hardware, antibiotics in irrigation fluid, and specific skin closure techniques. As a foreign body, shunts can also be infected by hematogenous spread. Rarely, spontaneous bacterial infection can occur years after any shunt manipulation from translocation of gut bacteria. The treatment of shunt infection typically involves externalization of the shunt accompanied by appropriate antibiotics that cross the blood-brain barrier and then replacement or internalization of the shunt.

ENDOSCOPIC PROCEDURES. Endoscopic third ventriculostomy can provide CSF diversion without an implanted device. The endoscope is typically inserted through a frontal burr hole, and an opening is made in the floor of the third ventricle to allow CSF to flow directly into the basal cisterns.[27] Endoscopic third ventriculostomy is ideal for obstructive hydrocephalus in carefully selected patients. In addition to requiring anatomy amenable to endoscopic third ventriculostomy, patients should not have risk factors for an additional component of communicating hydrocephalus. The endoscopic third ventriculostomy success score was developed to predict the odds of successful management of CSF diversion via endoscopic third ventriculostomy.[28] Importantly, because endoscopic third ventriculostomy can fail, albeit much less often than shunts, individuals treated with endoscopic third ventriculostomy typically require similar routine follow-up care as those treated with shunts.

In some individuals, endoscopic third ventriculostomy is combined with choroid plexus cauterization to reduce CSF secretion. In carefully selected patients, endoscopic third ventriculostomy and choroid plexus cauterization may offer benefits, especially for some types of postinfectious hydrocephalus in Africa.[29] A large multisite prospective study in the United States showed that

KEY POINTS

- Initial clinic visits to establish care for individuals with surgically treated hydrocephalus are opportunities to share communication options and expectations, reinforce symptoms and signs of elevated intracranial pressure, and review baseline imaging.

- Permanent ventricular shunts are composed of a ventricular catheter, a valve to regulate flow, and a distal catheter. Numerous types of valves exist, and no valve is superior to another type in multiple, well-executed trials.

- Most shunt malfunctions in childhood-onset hydrocephalus are caused by occlusion of the ventricular catheter. Common symptoms are intractable headache, emesis, and lethargy.

- The diagnosis of shunt malfunction is clinical and not solely based on imaging studies. At the time of shunt malfunction, ventricular size does not change on brain imaging in 20% of patients.

- Endoscopic third ventriculostomy fails less often than shunts, but these individuals still require routine follow-up care similar to those treated with shunts.

endoscopic third ventriculostomy and choroid plexus cauterization had a much lower success rate (22%) in individuals with posthemorrhagic hydrocephalus of prematurity.[30] Additionally, patients older than 1 year (corrected for gestational age) were more likely to have successful treatment.[30]

Soon after endoscopic third ventriculostomy and endoscopic third ventriculostomy with choroid plexus cauterization became widely used, it was noted that patients treated with endoscopic third ventriculostomy experience ICP normalization and symptom resolution, but the ventricles may not be decompressed. In general, aside from severe cases of hydranencephaly, there is a

CASE 11-2

A boy was born at 26 weeks gestation and had a bilateral grade III intraventricular hemorrhage. He developed posthemorrhagic hydrocephalus of prematurity and underwent a temporary shunt insertion. He had a permanent shunt inserted 15 weeks after birth (FIGURE 11-3) and, 3 months after that, presented with 2 days of reduced activity that progressed rapidly over hours to bradycardia and lethargy. Brain MRI showed marked dilation of the lateral ventricles. At surgery, the valve was found to be occluded and was replaced with a programmable one, with good clinical recovery. At age 6 years, he presented with several days of headache and irritability. Although it was a markedly different prodrome from what occurred with his first shunt malfunction, he was found to have an abdominal pseudocyst and distal shunt infection. Brain MRI at that time did not show ventricular enlargement.

COMMENT

Complete shunt catheter occlusion is often characterized by rapid clinical deterioration, as occurred in the first year of life for this patient. The later occurrence of spontaneous shunt infection more than 5 years after any surgical manipulation of the shunt is rare but highlights that ventricular caliber does not change in up to 20% of cases of shunt malfunction. Brain imaging alone is not sufficient to exclude a shunt malfunction.

lack of correlation between ventricular volume and cognitive outcomes. Large, well-executed prospective studies demonstrated that the amount of brain parenchyma is much more important for cognitive outcome than ventricular size.[31,32] One could argue that a ventricular shunt siphons off trophic factors, whereas endoscopic third ventriculostomy with choroid plexus cauterization limits the secretion. The ongoing multisite randomized controlled trial Endoscopic Versus Shunt Treatment of Hydrocephalus in Infants is attempting to determine cognitive outcomes after shunt versus endoscopic third ventriculostomy and choroid plexus cauterization.[33]

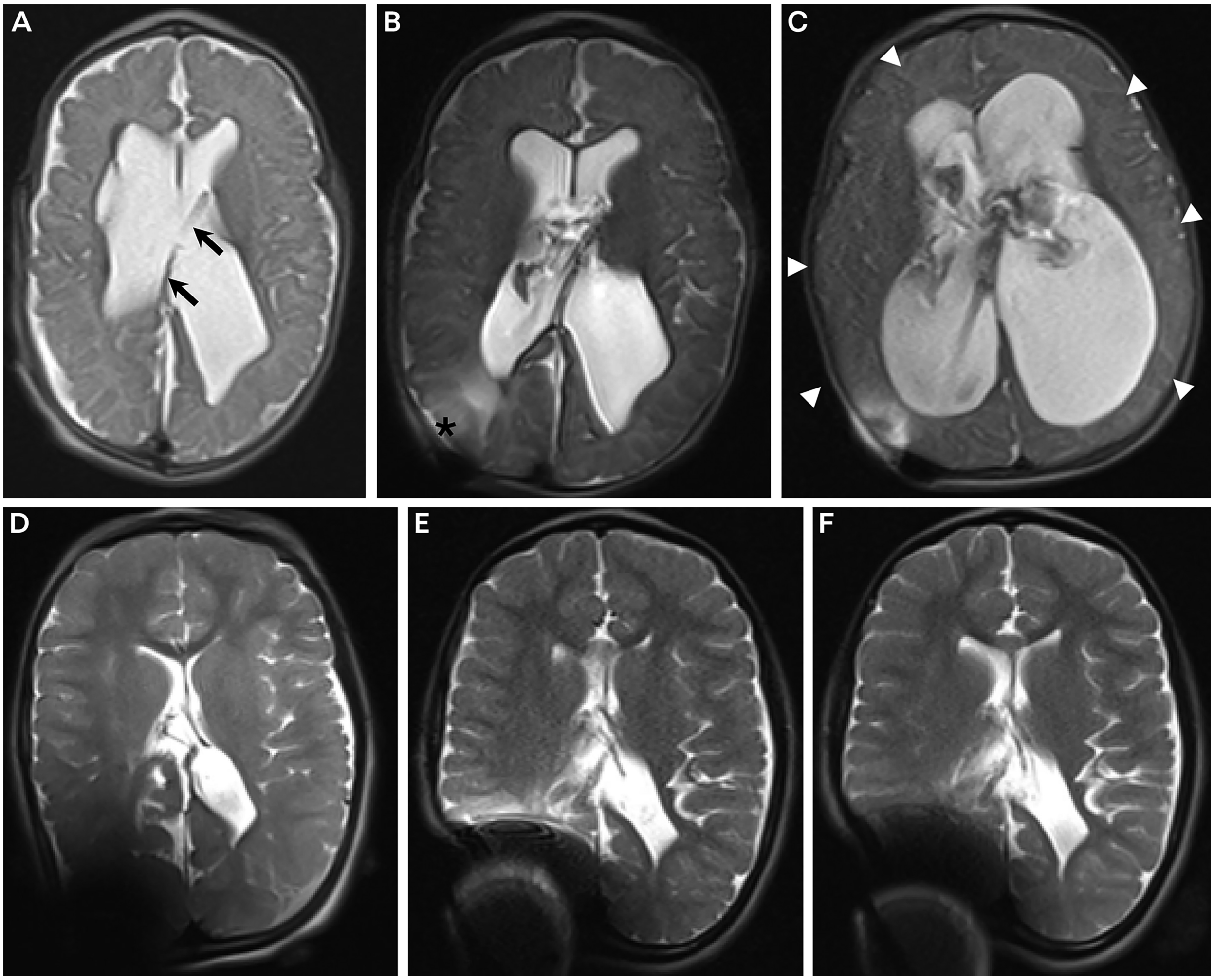

FIGURE 11-3

Serial axial T2-weighted MRIs from the patient in CASE 11-2. *A*, Baseline axial MRI after permanent shunt (*arrows*) insertion at approximately 3 months old. *B*, Surveillance scan at 1 year old. Note the interval expansion of the cortical mantle. The artifact in the right occipital area is from a fixed pressure valve (*asterisk*). *C*, Ventricular dilation was seen at the time of proximal catheter obstruction. Note the marked reduction in subarachnoid spaces around the perimeter (*arrowheads*). *D*, Surveillance image from a few years later. *E*, Distal shunt malfunction was not associated with ventricular dilation. *F*, New baseline image after treatment of the distal shunt malfunction.

HEALTH DISPARITIES

Health disparities impact the care of individuals living with childhood-onset hydrocephalus. Disparities in access to care have many root causes that are particularly apparent when the only current treatment is surgical. Globally, there are obstacles to seeking care, reaching care, and receiving definitive care.[34] Children with posthemorrhagic hydrocephalus of prematurity are prone to more shunt malfunctions than other etiologies of infantile hydrocephalus.[35] In a study of almost 1700 children in the National Spina Bifida registry, Black and Hispanic children had a lower rate of shunt malfunction than White children.[36] Retrospective analysis of the Kids' Inpatient Database revealed that African American children have a higher rate of nonroutine discharge after a CSF shunt procedure.[37] The causes of disparities are multifactorial and additional efforts are critical to reduce disparities.

ADULTS LIVING WITH CHILDHOOD-ONSET HYDROCEPHALUS

The transition from pediatric to adult health care can be challenging to navigate for individuals with hydrocephalus. Since patients were young or acutely ill at the time of their shunt malfunctions in childhood, many do not recall important details. Encouraging caretakers to provide a documented history is important. Applications for use in mobile devices can help patients and their families collect essential information to keep with them as they travel or change institutions.

Whenever possible, individuals with surgically treated hydrocephalus should establish neurosurgical care as part of their routine health maintenance. The clinical practice for providing routine care varies across regions and institutions. Ideally, care is established before upcoming medical events, such as pregnancy or elective surgery. Many individuals with childhood-onset hydrocephalus have other comorbidities and their hydrocephalus care may be provided as part of a multidisciplinary team. Adults living with childhood-onset hydrocephalus experience numerous other comorbidities, including epilepsy, sensorimotor impairment, chronic pain, and cognitive concerns. Although a healthy dose of caution about shunt malfunction is warranted, these other neurologic conditions often become more prominent with age.

KEY POINTS

- **Patients and their families should be encouraged to maintain a document with shunt details, including surgical dates, device details, presence of infection, and recent adjustments. Retaining brain imaging studies at baseline and at the time of malfunction are invaluable and mobile applications are now available for this purpose.**
- **People with hydrocephalus who are considering pregnancy are encouraged to establish care with a hydrocephalus team before becoming pregnant, if possible.**

CONCLUSION

Although some components of childhood-onset hydrocephalus have not changed substantially over the past several decades, new insights into pathophysiology, better treatment options, and best practices have markedly changed the outcomes for infants and children diagnosed today with hydrocephalus. We anticipate further progress toward nonsurgical therapies and improved surgical outcomes in the future to reduce the burden of hydrocephalus and related comorbidities.

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